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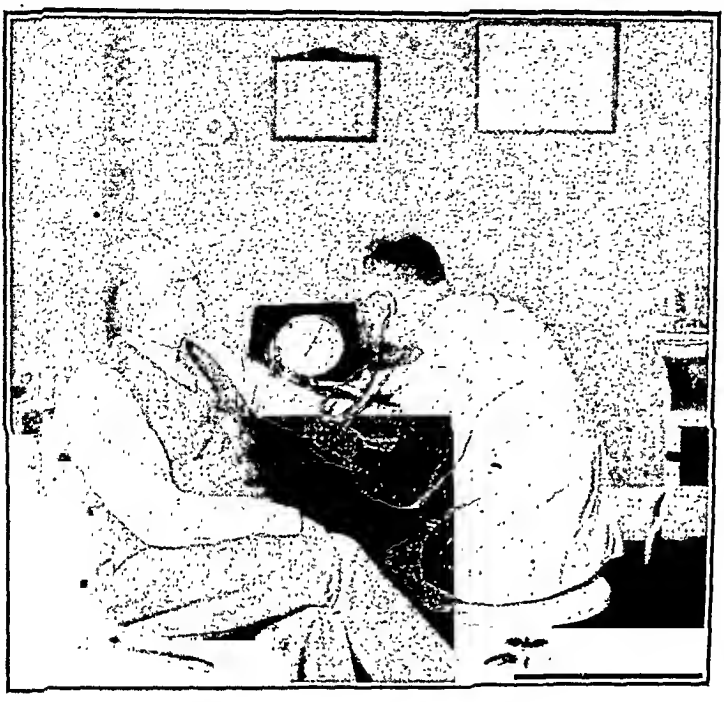

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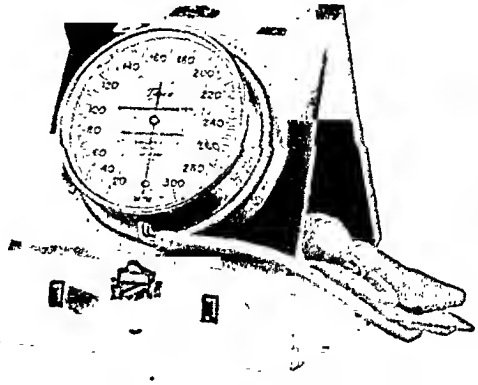

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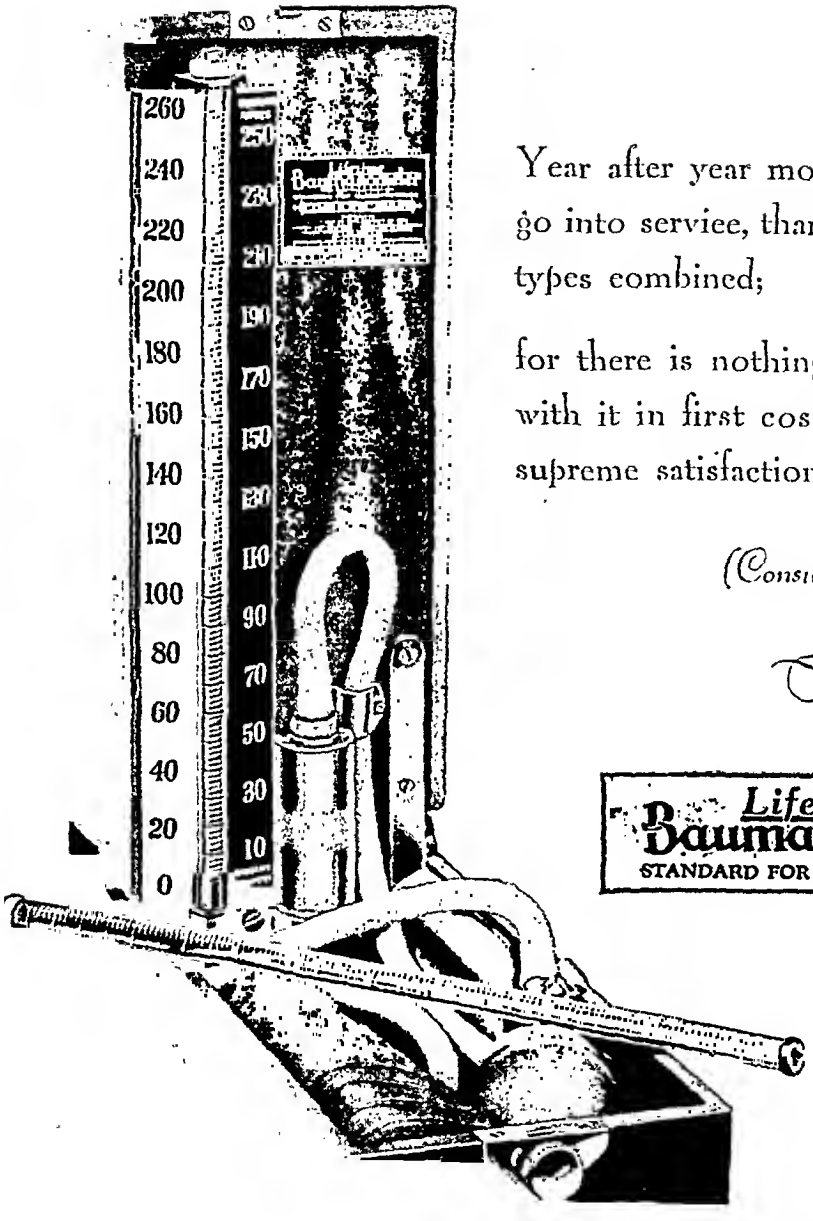

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SEPTEMBER, 1928

ORIGINAL ARTICLES.

THE CLINICAL APPLICATION OF THE PATHOLOGIC PHYSIOLOGY OF THE EXTERNAL SECRETIONS OF THE LIVER AND PANCREAS.

By C. W. McClure, M.D.,

BOSTON.

(From the Gastrointestinal Division of the Department of Biochemistry, Evans Memorial.)

The present communication is a correlation of results of a series of investigations on the aid obtained from examinations of duodenal contents in the diagnosis and treatment of organic and functional conditions affecting the liver and pancreas.

Examination of duodenal contents did not come into prominence until popularized by the noteworthy observations of Lyon,[1] which have stimulated numerous investigations on the clinical value of examinations of duodenal bile. Of the various reports which followed, that of Jones[2] is probably the most comprehensive. His study may be considered as authoritative, and demonstrates that the microscopic findings in duodenal bile are of clinical significance. His findings have recently been confirmed by Piersol, Bockus and Shay.[3] The investigations stimulated by Lyon's observations emphasized both the paucity of methods and the need for those suitable for examining the secretions and excretions which may be obtained from the human duodenum by means of a sound. Because of this, the author was encouraged to continue the development of methods and procedures for such examinations. For this purpose it was necessary first to establish the usual physiologic mechanisms concerned in the stimulation of biliary and external pancreatic secretory activities. In man it was found that the products of

food digestion were the usual stimulants to both activities.[4] In the course of animal studies[5] it was demonstrated that, under suitable experimental conditions, introduction of the products of food digestion into either the femoral or mesenteric veins would stimulate both the biliary and external pancreatic secretions. These observations on animals fully confirmed those made on man. Of the various food products, oleic acid was found most suitable for use in the procedure[6] developed for collecting specimens of duodenal contents for analysis. Methods applicable to the clinical laboratory were developed for demonstrating the activities of the pancreatic digestive enzymes[7] and for quantitating the concentration of bile acids,[8] of total substances giving the Pettenkofer reaction,[9] of total pigments,[8] of two classes of pigments[10] normally found in bile and of cholesterol.[10]

Initial observations[11] on 15 normal subjects established the activities of the pancreatic enzymes present in duodenal contents. Later, these observations were fully confirmed by studies made on 10 normal subjects by Jones.[12] Subsequent to the work of Jones, the author has added confirmation to all these observations by a study of a much larger series of control observations. The results of studies[13] made on the enzymic activities of duodenal contents in patients with unquestionable disease of the pancreas, many of whom came to autopsy or laparotomy, established the clinical value of such determinations. The results of these studies were confirmed later by observations on a much larger number of patients. Sufficient numbers of observations have been made definitely to eliminate the various sources of error which were theoretically objectionable. When the proper portion of duodenal contents has been collected and the analytical methods have been correctly performed the results obtained give uniformly reliable information concerning the external secretory activities of the pancreas.

Studies were made on the duodenal bile collected by the procedure and analysed by the methods[7, 8, 9, 10] devised by the author. The earlier observations established minimum normal limits[6, 10] for the concentrations of the various substances quantitated. The correctness of these limits was subsequently confirmed by observations on over 200 control subjects. In order to establish relatively uniform maximum limits of variation for these concentrations it would be necessary to restrict the patient's habits temporarily to a prescribed set of experimental conditions. Obviously, such would interfere seriously with the practical application of examination of duodenal bile. Fortunately, observation has established that such restrictions are unnecessary if interpretation of the abnormal findings is limited to those which fall below the demonstrated minimum normal concentrations. These latter are given in the following table:

CHARACTER OF THE BILE MOIETY OF DUODENAL CONTENTS FROM NORMAL AND ABNORMAL SUBJECTS.

Case No.	Furfurol. No.	Cholesterol, mg. per 100 cc.	Alcohol-insoluble pigment, mg. per 100 cc.	Alcohol-soluble pigment, mg. per 100 cc.	Color.	Remarks.
	100	30.0	7.0	8.0	Brown	Minimal normal limits.
1	106	65.8	Tr.	Tr.	Yellow	Migraine.
2	Tr.	39.4	6.7	2.6	Brown	Migraine; cholecystotomy for gall stones.
3	44	31.9	4.9	3.7	Light brown	Migraine.
4	52	Tr.	9.5	9.4	Brown	Catarrhal jaundice during recovery; icterus still well marked.
5	68	45.6	3.4	4.7	Light brown	Toxic jaundice (arsenic) six weeks after jaundice had disappeared.
6	Tr.	27.3	2.5	3.5	Yellow	Chronic cholecystitis; before operation.
7	50	28.1	10.0	9.6	Brown	Cirrhosis of marked degree; no icterus.
8	0	0	0	0	White	Cancer head of pancreas; deep icterus; very little pancreatic enzymes; laparotomy.
9	0	0	0	0	Colorless	Complete obstruction to common duct; normal pancreatic enzymic concentration; laparotomy.
10	Tr.	Tr.	5.4	3.0	Light brown	Cirrhosis of liver; deep icterus, ascites; slightly abnormal pancreatic function; laparotomy.

The earlier observations on the analysis of duodenal bile of patients with various hepatic affections were subsequently confirmed by comprehensive studies of the duodenal bile of over 500 such patients. Representative findings are outlined in the table. All these studies established that when the proper portion of duodenal bile had been collected and the analytical methods correctly performed the results yielded uniformly reliable information concerning the functional activity of the liver.

Lyon's observations on duodenal bile served to emphasize the uncertain state of knowledge concerning the mechanisms by which bile gains entrance to the duodenum. Lyon had accepted as correct the theory advocated by Meltzer that relaxation of the sphincter of Oddi was accompanied by contraction of the gall bladder, causing emptying of its contents. Subsequent to Lyon's publications a number of investigators studied the action of the gall bladder. The diverse conclusions drawn from the results of these studies are outlined by McMaster[15] and are comprehensively discussed by Giordano

and Mann,[16] to whose articles the reader is referred. McMaster developed ingenious experiments which permitted simultaneous observations on pressure relations in the gall bladder and various parts of the system of bile ducts with but little disturbance of normal relations. His observations demonstrated that Meltzer's theory, mentioned above, is essentially correct. McMaster demonstrated, apparently conclusively, that by increase of its own muscle tone the gall bladder ejects bile at intervals during the process of gastric digestion. However, he states: "It is of importance to note, too, that only a *little bile* was ejected at any one time." Apparently the contractions observed by McMaster were too slight to be visible by mere ocular observations of the gall bladder. McMaster demonstrated that during the progress of food digestion the activity of the gall bladder of dogs modified the character of bile which would normally have entered the duodenum. The observations of McMaster on dogs apparently support the assumption of Lyon and subsequent investigators that duodenal bile, collected after placing magnesium sulphate directly in the human duodenum, could be divided into two portions. One portion of such duodenal bile is of yellow color and was assumed by Lyon to have come directly from the liver. The yellow color was considered to be the result of the bile not having been concentrated by action of the gall bladder. The other portion is of dark color (brown) and was assumed to be concentrated bile coming directly from the gall bladder. Lyon and others found an absence of this dark (brown) bile in the presence of chronic disease of the gall bladder. The observations stimulated studies[17] on the relation between the absence of this dark bile and impairment of function of the gall bladder as demonstrated by the well-known Graham Roentgen-ray procedure. The results of these observations and studies led to the conclusion that absence of dark duodenal bile is due to impairment of functional activity of the gall bladder.

The statements that dark duodenal bile originates exclusively in the gall bladder and that the abnormal yellow bile is due solely to gall bladder inactivity are of too great clinical significance to go unchallenged. By the use of the procedures and methods devised by the author, the character of bile from any source can be determined with a greater exactness than has heretofore been possible. Using these methods, two classes of pigments have been found to be present in normal bile, and their amounts can be readily quantitated.[10] In alcohol, certain classes of these pigments are soluble, while another class is apparently totally insoluble. One class of alcohol-soluble pigments is yellow in color, the alcohol-insoluble class is dark brown. It is the latter which imparts the dark color (dark brown) to bile, whether obtained from the duodenum, gall bladder, common duct or the hepatic ducts. Analysis of pale yellow duodenal bile obtained in pathologic states of the liver has

frequently demonstrated a high degree of pigment concentration as compared with this class of bile pigments found in control subjects. Frequently such yellow biles show a high concentration of cholesterol, and sometimes of the furfurol reacting substances. (Compare Case 1 of table.) In such bile there is little or no alcohol-insoluble pigment. Under treatment the alcohol insoluble brown pigment may eventually reappear and may finally reach such a degree of concentration as to impart the dark (brown) color to the duodenal bile. After cessation of treatment the duodenal bile may again revert to its original pale yellow pathologic type; treatment will again cause the reappearance of the alcohol-insoluble pigment, and the duodenal bile will again become of dark (brown) color. Comparable observations have been made on the concentration of the furfurol-reacting substances and of cholesterol of abnormal duodenal bile. Pathologic duodenal biles are often found in which all the elements are present in low degree of concentration. Under treatment one or two elements, cholesterol or alcohol-soluble pigment, as a rule, first begin to increase. Under these circumstances these one or two elements may eventually reach a high degree of concentration before the other elements show appreciable change in their concentration. The other elements may or may not eventually reach a high degree of concentration. Such findings demonstrate that the yellow bile (the liver bile of Lyon) is not merely a product of dilution.

Findings comparable to those described above have been demonstrated on a large number of subjects through analyses numbering in the hundreds. Of these patients, sufficient numbers came to operation to demonstrate that all the changes described in duodenal bile occur in the presence of marked chronic cholecystitis, both with and without cholelithiasis. Therefore, concentrated duodenal bile of dark (brown) color can be made to appear in the presence of such marked disease of the gall bladder that it is fair to assume the functional activity of that organ was much impaired.

The abnormal yellow duodenal bile (liver bile of Lyon) has been collected from a group of patients whose gall bladders reacted normally to sodium tetraiodophenolphthalein. The dye was given orally, in every instance the gall bladder being plainly outlined on the Roentgen ray film and showing a marked degree of concentration one hour after a fat meal. The abnormal yellow bile was collected on numerous occasions from each of these patients, in order to rule out an exceptional result. Two of the patients underwent cholecystectomy. The gall bladders of both patients were normal grossly and microscopically, while bacteriologic examination of their contents and walls were negative. These findings negative the assumption of Lyon and others of a necessary relation between impaired gall bladder activity and abnormal duodenal bile of yellow color.

The only apparent phenomena which can explain the author's

findings, described above, are those related to the secretory and excretory activities of the liver. It is, therefore, concluded that under the proper set of experimental conditions the obtaining of only yellow bile from the duodenum results from disturbance in the state of liver function.

A group of patients has been studied who had relapsed after cholecystectomy. The duodenal biles of these patients were very abnormal. Under treatment these biles returned eventually to a much more normal state. Frequently all elements, except the alcohol-insoluble pigment, would become of normal concentration. The alcohol-insoluble pigment was usually absent from the duodenal biles during the first weeks of treatment. Then this pigment would reappear and gradually increase in concentration; but, usually, such increase would not reach more than 60 per cent of the normal. These findings show that progressive increase in the concentration of duodenal bile may occur in the absence of the gall bladder. The only apparent explanation for this phenomenon is greater functional activity of the liver.

The results of the author's findings, discussed above, show beyond reasonable doubt that dilution of the bile is not a source of error when that bile has been properly collected for analysis. Obviously the proper portion of duodenal contents must be collected if the analytic results are to be of any significance, either as to the functional activity of the liver or of the pancreas. For this reason it is emphasized that the proper execution of the procedure for collecting duodenal contents requires a considerable amount of experience. Also, and very unfortunately, the analytic methods are not without their technical difficulties. The findings show further that abnormal duodenal bile may occur in the presence of gall bladders apparently functionally unimpaired; on the other hand, normal or nearly normal duodenal bile may be obtained in the presence of marked functional impairment of the gall bladder or in the absence of that organ. These findings indicate that functional activity of the gall bladder does not appreciably influence the results obtained in duodenal biles collected by the procedure and analysed by the methods devised by the author.

The above conclusion is not antagonistic to the observations on animals. Both McMaster[15] and Burget[16] have demonstrated that the gall bladder of a dog ejects bile, but only in minimal amounts, during digestion. The amount so ejected was apparently too small for its demonstration by Auster and Crohn.[17] It is difficult to understand how such small amounts of bile could appreciably influence the physical characteristics of the much larger amount of bile continuously secreted by the liver. Nevertheless, McMaster's observations on dogs showed apparently such an influence. Working under entirely different experimental conditions, Mendenhall and McClure[20] were unable to demonstrate any influence of gall

bladder activity on the character of bile secreted by cats. If such a physiologic difference actually exists between dogs and cats, it is conceivable that the action of the gall bladder of man may not exert much influence on the character of bile entering the duodenum during digestion.

Rous[21] has found that "after hepatic or ductal injury (in dogs) a great deal of organic débris of various sorts may be present in bile . . . particles of the material of which 'bile thrombi' are composed may be found in the bile." He further reports "there are to be found in the secretion (bile) after many sorts of hepatic injury little nuclei . . ." These nuclei consist of a mixture of calcium bilirubinate and carbonate. These abnormal findings in the bile of dogs after hepatic injury may be correlated with the author's observation that functional impairment of the liver accompanies chronic cholecystitis in man. Such correlation permits the suggestion that possibly the reported microscopic findings in pathologic duodenal biles from man are due to the character of the bile secreted by an abnormally functioning liver rather than to disease of the gall bladder. Furthermore, there is no histologic reason why the so-called "gall bladder epithelium," found in abnormal duodenal bile, could not be from the mucosa of the bile ducts or duodenum. Bile stains epithelium from any source, and there is bile constantly present in the biliary ducts and duodenum. Therefore, any epithelium present there will be stained by bile just as much as will epithelium coming from the gall bladder. Bacteriologic findings in duodenal bile, for obvious reasons, have questionable significance as to the origin of any organisms found. Indeed, Branch[22] finds that in chronic cholecystitis neither the bile or gall bladder walls are infected as a rule. These observations and the conclusions drawn from the results of the author's studies on duodenal bile, discussed above, indicate that the microscopic findings in abnormal duodenal bile are not necessarily the result of gall bladder disease but may result from associated abnormal conditions.

Both the concentrations of pancreatic enzymes and of the various biliary constituents can be determined in the proper portion of duodenal contents collected after stimulation of the liver and pancreas by oleic acid. The enzymic concentrations of the pancreatic moiety fall into three groups, as follows:

1. Normal concentrations are found in all conditions in which the functional activity of the head of the pancreas is unimpaired.

2. Abnormally low concentrations are found in lesions including the ampulla of Vater, lesions involving the head of the pancreas and in acute or chronic pancreatitis.

3. An intermediate value between normal and abnormally low concentrations is characterized by normal concentrations of one or two enzymes, while that of the other one or two is much diminished below the minimum normal; that is, dissociation of the secretion of

the various types of enzymes occurs. This is found in convalescence from acute pancreatitis, in chronic pancreatitis, in functional impairment accompanying partial occlusion of the ampulla of Vater and also during stages of destructive lesions involving the head of the pancreas. Jones[12] demonstrated such dissociation in diabetes mellitus.

Determination of liver function by duodenal analysis is useful in the diagnosis of that group of patients whose symptoms resemble those of the gastrointestinal neuroses, yet in whom there is liver functional disturbance. It is useful also in the diagnosis of a group of patients in whom there is disturbed liver function and whose symptoms more or less closely resemble cholecystitis or peptic ulcer; yet neither lesion exists. Such symptoms represent the clinical entity, which should be more familiar to physicians, of migraine with abdominal symptoms; the migrainous headache may or may not occur. Nausea, vomiting, anorexia, dyspeptic symptoms, persistently relapsing duodenal ulcer, hepatic fever with jaundice and with or without pain which may follow cholecystectomy, and migrainous attacks have all been found to be frequently associated with abnormal hepatic function, as shown by analysis of duodenal bile.

It must be emphasized that the variations in the concentrations of the biliary components are not directly of causal significance; for example, a low cholesterol output does not imply that the retention of this substance causes damage to the hepatic cells or to those of any other part of the organism. The biliary components determined are end results of highly diverse metabolic activities. The changes in their amount and character are connected with underlying diseased conditions of which they are but expressions. Therefore, the results of duodenal bile analyses are not diagnostic in themselves. They merely add to the data obtained by the various other clinical examinations. For this reason their clinical significance varies in the individual patient.

The combined study of the biliary and pancreatic moieties of duodenal bile is of value in differentiating between benign and malignant causes for jaundice and in localizing the site of the lesion. The important findings in such differentiation may be outlined as follows:

1. Normal enzymic concentrations and no bile demonstrate that the lesion is in the biliary tract above the ampulla of Vater. If bile reappears after repeated instillations of magnesium sulphate solution into the duodenum it is highly probable that the obstruction to the biliary tract is of benign character. The more concentrated the bile that is obtained, the more probably benign is the lesion. But if bile does not reappear, the chance that the lesion is benign is much more remote.

2. Abnormal enzymic concentrations, with the initial presence of bile, especially if the bile is relatively concentrated, or if it reap-

pears after intraduodenal instillation of magnesium sulphate solution, suggest benign obstruction in the region of the ampulla of Vater. In such cases the reappearance of bile may be accompanied by increase in enzymic concentrations.

3. Abnormal enzymic concentrations, when bile remains absent from the duodenum in spite of repeated intraduodenal administration of magnesium sulphate, suggest cancer of the head of the pancreas.

4. Duodenal contents grossly discolored with blood, with abnormal enzymic concentration and containing no bile denote cancer involving the head of the pancreas, common bile duct and wall of the duodenum.

Obviously, the findings described are not often diagnostic in themselves, but they are diagnostic aids. By their use in selected cases diagnosis may be made before laparotomy, which otherwise could not be made until after operation.

The following incident will illustrate a common application of the findings outlined above. A well-preserved man, aged seventy-seven years, sought medical consultation because of the onset of "painless" jaundice. The symptomatology was typical of that group which is most often due to cancer of the head of the pancreas. Exhaustive examinations failed to uncover cause other than cancer for the jaundice. But the duodenal contents showed the following: The contents were of dark (brown) color, furfurol number was 52, cholesterol a trace only, alcohol-insoluble pigment 9.5 mg. and alcohol-soluble pigment 9.4 mg. The enzymic activities were proteolytic 3 mg., amylolytic 2 mg. and lipolytic 1.5 cc. Thus, although there was definite evidence of liver functional disturbance, the duodenal contents showed patent bile ducts and that there was no obstruction to the flow of pancreatic juice. These duodenal findings almost certainly ruled out cancer of the head of the pancreas. These findings, together with the other examinations, allowed the diagnosis of benign cause for the jaundice to be made with a high degree of certainty. The subsequent progress of the patient proved such a diagnosis to be correct.

Since the liver's functional activity governs the character of bile produced, analysis of duodenal bile permits the determination of the effect of therapeutic measures on the biliary function of the liver. Under such experimental conditions the author investigated the action of magnesium sulphate on the biliary system of man. It was found that intraduodenal administration of this salt would oftentimes eventually be followed by changes in duodenal bile from abnormal to normal, or nearly normal, character. Therefore, it was concluded that magnesium sulphate probably exerts such pharmacodynamic action on the hepatic cells as to change abnormal to more normal functional activity. This conclusion is supported by the studies of Mendenhall and McClure.[20] These studies

were carried out on dogs and cats. The results seemed to demonstrate that magnesium sulphate stimulated the production of bile by the liver cells. However, such stimulation was produced only when the proper concentration of the salt reached the liver. If administered by mouth the gastric secretion not only dilutes the solution, but also it is delivered in relatively small amounts into the intestines. It is, consequently, absorbed from the intestines in low degrees of concentration. For this reason the magnesium sulphate does not reach the liver in a degree of concentration capable of producing the desired pharmaeodynamic action on the liver cells. Large numbers of observations on patients show that the intraduodenal administration of the salt permits its absorption in that degree of concentration which produces favorable results. The treatment of patients can best be controlled by analysis of the duodenal bile at frequent intervals throughout the course of such therapy.

Intraduodenal therapy has been controlled in the manner suggested in groups of patients with the following clinical conditions and whose duodenal bile analysis showed the presence of liver functional disturbances: (*a*) Migraine;[23] (*b*) chronic cholecystitis; (*c*) return of symptoms after cholecystectomy or cholecystotomy; (*d*) chills, fever, jaundice and often pain stimulating gall-stone colic which may eventually follow cholecysteetomy or cholecystotomy; (*e*) symptoms of various gastrointestinal neuroses; (*f*) persistently relapsing duodenal ulcer. Very favorable clinical results have been obtained in a relatively large experience with these groups, when the treatment was controlled as described. The most surprisingly favorable results have been obtained in those patients who developed eventually hepatic fever, jaundice and pain subsequent to cholecystectomy. Also, patients with toxic, infectious or catarrhal jaundice responded well to this type of therapy. It is essential that subjects who are to receive this type of therapy should be carefully selected. The author makes it a rule to treat only those whose complete clinical picture justifies the conclusion that presenting symptoms are probably due to an actually demonstrated hepatic dysfunction. Obviously, patients demanding surgical intervention should not be given such treatment.

During the treatment of the conditions enumerated above it was noted that improvement in clinical symptoms frequently coincided with the return of the duodenal bile to more normal character. This coincidence was so frequent as to justify the conclusion that many of the symptoms relieved were an expression of the liver's functional state. Certainly there is no other apparent basis than correction of liver functional disturbance which will explain the action of magnesium sulphate in relieving attacks of fever, jaundice and pain which may follow cholecystectomy. Anorexia, nausea, vomiting, bloating, belching are all symptoms com-

mon to chronic eholeeystitis. Their frequent relief following intraduodenal treatment with magnesium sulphate indicates that many of the symptoms eommonly ascribed to disease of the gall bladder are in reality due to the associated functional disturbanee of the liver.

The types of funetional disturbances of the liver whieh have been discussed are considered to be the result of underlying pathologic states. Since "as temporary injury increases, permanent injury also inereases,"[24] it is readily coneeivable that underlying pathologie states can cause varying degrees of damage to the hepatic eells. Such variation in damage is probably an important faetor governing the degree of dynamic equilibrium to whieh the individual patients' liver cells can be returned by treatment. Following cholccystectomy, not only this faetor but also altered mechanical conditions may possibly affect, qualitatively if not quantitatively, the activities of the liver cells. Both these factors offer explanation for the frequent failure of the alcohol-insoluble pigment of duodenal bile to reach more than 60 per eent concentration after removal of the gall bladder.

The results of the investigations diseussed above demonstrate that the favorable elinieal results obtained by intraduodenal administration of magnesium sulphate are due to its aetion on the liver cells and are probably not due to drainage of the gall bladder as eontended by Lyon and subsequent investigators. Indeed, the observations of McMaster[15] and of Mendenhall and MeClure[20] on animals, and of Whitaker[25] on man make it highly probable that "biliary drainage" of the gall bladder does not result from stimulation of magnesium sulphate. Therefore, the commonly used terms "biliary drainage" and "duodenal lavage" are misnomers and are misleading.

Summary. 1. Many of Lyon's findings in pathologic duodenal contents are thought by the writer to be of clinical significance. He does not agree, however, with the explanation of the pathologic physiology which Dr. Lyon offers for these findings. Evidence has been presented by the writer which apparently demonstrates that the findings in duodenal bile are essentially the result of the state of functional activity of the liver rather than of the gall bladder.

2. Evidence is also presented demonstrating the uniform reliability of the procedures for collecting and of the methods for analysing duodenal contents for the enzymie concentrations and the eoneentrations of the biliary components.

3. The estimation of enzymic activities affords an index to the state of external pancreatic function; the determination of the eoncentrations of biliary components gives an index to the state of hepatic function.

4. The necessity of learning what portion of duodenal contents to collect and how to execute properly the analytical techniques is

emphasized. The clinical use of these examinations has been discussed and outlines of them for clinical purposes have been given.

5. Evidence has been presented on which is based the conclusion that certain clinical entities and clinical symptoms result from disturbances in the state of functional activity of the liver. In selected cases the intraduodenal administration of magnesium sulphate solution will tend to correct abnormal hepatic function and thus relieve the symptoms which arise from it.

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THE VALUE OF ROUTINE ESTIMATIONS OF BLOOD BILIRUBIN.

With a Report of 567 Cases Including a Group of Unrecognized Toxic Hepatitis.*

By Joseph S. Diamond, M.D.

Attending Gastroenterologist Sydenham Hospital, New York.

The multiplicity of the normal physiologic functions of the liver and especially its large power of reserve render it exceedingly hazardous to single out one special functional test as a diagnostic measure of a more generalized liver dysfunction. It must be admitted, however, that bile pigment formation is one of the important functions of the liver and that the very term bilirubin is synonymous with hepatic activity, whether the bilirubin be a direct metabolic product of the Kupffer cell, or merely an excretory component of the bile brought to it from remote sources in the body. While we are aware of the diversity of the functions of the liver and

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that each one may be affected separately or in different degrees it has, nevertheless, been the experience that a high blood bilirubin is frequently associated with other functional disturbances and that the blood bilirubin estimation is a delicate test and can safely be utilized as an indicator of a more generalized pathologic process in the liver in the absence of hemolytic diseases.

In a comparative study of functional liver tests, the tests including the blood bilirubin, the phenoltetrachlorphthalein, the urobilinogen, galactose and levulose, we found with but few exceptions, the blood bilirubin most frequently affected.

The method employed was the van den Bergh reaction, checked up in many instances, with the icterus index. The advantages of the van den Bergh method are that it is uninfluenced by hemolysis and by the presence of lutеins and lipochromes, pigment substances introduced with the green vegetables and fatty foods which, in themselves, cause yellow discoloration of the serum as shown by Hess and Meyers.[3] This method also differentiates the types of jaundice through its direct and indirect reactions and is very sensitive in the latent icteric stage.

Using the original van den Bergh method, the standard for normal is from 0.4 to 0.8 units or 2 to 4 mg. per 1000 cc., one unit of bilirubin being equivalent to 5 mg. per 1000 cc. The modifications of Thannhauser and Anderson,[5] or Green, Snell and Walter,[6] as employed at the Mayo Clinic give higher figures, from 1 to 2.8 units (5 to 14 mg.) due to the more complete coupling of the azobilirubin since the reagent is added prior to the precipitation of the proteins by alcohol. It is of no particular advantage in the lesser forms of jaundice but has its use in the higher obstructive types of jaundice. In our series, we have employed the original method.

The material here reported was collected in part from the Bellevue Hospital (third medical division) in 1923 while working with Dr. Wallace on urobilinogen,[9] and more recently from the Sydenham Hospital. The chronic ambulatory cases represent, in the main, office patients. There were 567 cases in some of whom tests were repeated at different periods.

Hepatic Toxemia. The most valuable information in the use of the test was derived from a routine examination of chronic ambulatory patients who presented a certain train of toxic symptoms simulating the functional neuroses. There were 29 patients in this group who gave definite evidence of liver dysfunction as indicated by the high bilirubin values in the latent icteric stage. These were chiefly young adults between the ages of eighteen and thirty years who complained of general indisposition, fatigability, loss of ambition, nervousness, irritability, depression, digestive disturbances, and in some foul breath and coated tongue. Many of these could readily be mistaken for the functional neuroses. In fact, the majority of them had been so treated. Some had even been subjected to psy-

choanalysis. In many, a dietary indiscretion could be traced, such as the eating of canned fish or meats, the attack commencing with acute indigestion and vomiting. The blood bilirubin was high, varying from 1.5 to 4.8 units (7.5 to 24 mg.) approaching the kidney threshold for bile pigment. Only in 1 case was there a temporary appearance of bile in the urine. The urobilinogen in the urine was also high. These cases were carefully examined, the examinations including the gastrointestinal tract, the gall bladder, and all possible abnormalities ruled out.

The following case illustrates one of the milder forms of unrecognized toxic hepatitis:

Case Reports. CASE I.—M. G., student, aged twenty years, consulted me on April 20, 1927. Two months prior to this, the patient was suddenly awakened during the night with an attack of nausea, epigastric distress, vomiting, and marked general weakness. On questioning as to the possible cause of the indigestion, he stated that he had eaten a goodly portion of canned salmon for lunch. He remained at home for several days until his acute symptoms subsided and returned to school, though still feeling nauseated and feeble. As the days went by, he noticed that he could not return to his normal state. He could not concentrate or think clearly. He could no longer sit up at night to study as was his usual custom. He developed many neurasthenic symptoms and was finally forced to drop out from school. He consulted a number of physicians and a diagnosis of psychoneurosis and depression was made. When seen by me he was apathetic and considerably worried about his inability to continue his school work. He was sallow in appearance, the scleræ were of a yellowish tinge, he had a coated tongue and foul breath, and complained of nausea, poor appetite and lack of ambition. The liver area was tender. The examination of the gastrointestinal tract and gall-bladder series were negative. The urine contained an increase in urobilinogen, and the blood bilirubin was 2.5 units (12.5 mg.). The hemoglobin was 80 per cent and the red and white counts were normal. The diagnosis of hepatitis was made and a course of calomel and saline was administered along with a diet rich in carbohydrates and poor in proteins. His symptoms gradually began to subside and after a rest during the summer months was able to return to school in the fall. His blood bilirubin returned to normal (0.75 units).

It appears that in this group we have a definite clinical entity of liver toxemia induced by putrefactive proteins, which without the aid of the modern clinical methods, would be unrecognized and untreated. One might designate this group as hepatic toxemia due probably to a moderate toxic hepatitis.

Contrasting with these we have a large group of the psychoneuroses, the vagotonias, gastric neuroses, anxiety states, depression, comprising 63 patients in whom the blood bilirubin remained normal and whose condition could not be accounted for on the basis of liver toxemia. The belief in the so-called physiologic bilirubin elevation should be discarded. I have never encountered any elevation of the blood bilirubin in individuals entirely symptom-free. When present it must be regarded as due to hepatic dysfunction in the absence of hemolytic diseases.

There was also a group of 22 cases with intestinal stasis where the only symptom was marked constipation without any general symptoms. In these, the blood bilirubin was normal. Only in 5 instances, it was slightly above normal, 1 unit (5 mg.), and these were in cases of stasis with marked visceroptosis.

The increased blood bilirubin in the above series must be regarded as an index of a more generalized liver disturbance involving the protein metabolism which is probably responsible for the toxic symptoms. Unfortunately, we have developed no chemical tests which can give us an insight into the very important function of the protein metabolism, and the difficulty lies in the approach of the intermediary products of metabolism, the synthesis of the amino-acids into coagulable proteins and the detoxication of the amino bodies brought from the intestinal canal. The Widal hemoclastic crisis is but an indirect approach and is found in well advanced and outspoken pathologic lesions.

The treatment employed was chiefly eliminative and dietetic. Cathartics such as calomel were frequently administered along with salines and bile salts. The diet consisted of a rich supply of carbohydrates and a restriction in animal proteins.

The early recognition of hepatic disorders by clinical methods renders considerable advance to preventative medicine. The question arises whether this liver derangement may not be the precursor of the more chronic liver states and lead, if untreated, to the development of liver cirrhosis, a condition hitherto unrecognized. Those cases coming earliest under attention have shown a rapid improvement in the clinical symptoms, the blood bilirubin also returning to normal. While in those in whom the condition existed for several months, the progress was not as favorable, as illustrated in the following case:

CASE II.—S. Z., salesman aged twenty-four years, married, came under my observation on July 6, 1926. Three months previous to this he had been suddenly seized one afternoon, with an attack of syncope followed by distress, vomiting and retching. This lasted for twenty-four hours, the patient going off frequently into a faint. He remained in bed for several days and during the next three weeks had two more similar attacks of fainting and vomiting. He had never quite fully recovered, felt nauseated most of the time, lost weight, and could not work continuously although he made many attempts. Upon examination, he appeared sallow, the sclerae being distinctly yellow; his hemoglobin was 70 per cent; red count, 4,000,000 and the white count, 6400. The urine gave a 4+ indican reaction and the urobilinogen was markedly increased, 1 to 150 dilution. There appeared a minute trace of bile in the urine on one examination. The blood bilirubin was 4.8 units (24 mg.). The liver area was tender, the edge being palpable. The bromsulphonephthalein showed a 28 per cent retention in fifteen minutes and was negative in a half hour. A careful study of the gastrointestinal tract and gall bladder gave negative findings. A diagnosis of toxic hepatitis was made. The patient admitted having eaten canned meats for breakfast on the day of his attack. He was placed on eliminative and dietetic treatment and felt somewhat improved. He returned on December

20, 1926, feeling better, still complaining, however, of poor appetite, nausea, becoming easily fatigued, being unable to perform half his customary amount of work. He was less sallow and his blood bilirubin though still elevated, had come down to 2.5 units (12.5 mg.). The urine still contained urobilinogen and indican in increased amounts. Eliminative treatment was again resumed and caution as to overwork and food was advised. The patient again returned on March 20, 1927, after an exacerbation of his symptoms. The blood bilirubin was increased to 4.5 units (22. 5 mg.), the urine containing increased amounts of urobilinogen and indican. During the summer of last year, he felt much better, gained in weight, and worked more steadily. The patient was again seen during last November following another exacerbation of his symptoms. The findings were the same, the blood bilirubin being 4.4 units (22 mg.), the urine running high in urobilinogen and indican. The liver edge was now more plainly palpable and was tender. The spleen could not be felt although it was somewhat large to percussion.

This case illustrates the gradual transition from an apparently simple toxic hepatitis into the biliary cirrhotic group. The chronic course extending over a period of almost two years, the progressive enlargement of the liver, the frequent exacerbations during which periods the blood bilirubin rose to higher levels, and the increased urobilinuria, speak for the strong similarity to biliary cirrhosis.

Migraine. Another interesting group was the migraine,[7] the familial hemicrania and the abdominal migraine. There were 38 cases in 90 per cent of whom the blood bilirubin varied from 1 to 5 units (5 to 25 mg.).

I have drawn some analogy to Widal's hemoclastic crisis and regard this type of migraine as an allergic manifestation resulting from the inability of a deficient liver cell to metabolize animal proteins. In several instances, the symptoms of abdominal migraine have been mistaken for gall-bladder disease and have come to operation without in the least, however, influencing the symptoms. These attacks distinguish themselves by their character, commencing always with hemicrania gradually developing into the abdominal attacks. The high bilirubin points to hepatic dysfunction as a factor in this disorder.

Cholelithiasis and Cholecystitis. In the large groups of cholelithiasis and cholecystitis, the bilirubin estimation in the serum was not of great value unless made during or shortly after an acute attack. The increased blood bilirubin during the acute attack must be considered not always as due to spasm or temporary obstruction of the duct, but more in the light of a functional disturbance of the hepatic cells, an inhibitory phenomenon, analogous somewhat to the functional sympathetic anuria occurring in the opposite kidney when a ureter is obstructed.

There were 56 cases of cholelithiasis. The diagnosis was reached by the positive radiographic findings along with clinical symptoms. Many of these came to operation. The bilirubin was increased in 18 cases, varying from 1.3 to 5.5 units (6.5 to 27.5 mg.). Ten of

these were examined during an acute attack. The bilirubin was above two units. Three had stones in the common duct and their bilirubin was 4, 5 and 5.5 units respectively. I did not include in this group the acute surgical cases with jaundice as in these the diagnosis was self-evident.

There were 98 cases of cholecystitis. The diagnosis was not quite as simple in this group. Conclusions were reached from the positive clinical history and from the poor or no filling of the gall bladder by the Graham method. While there may be a certain percentage of error in this group, as fewer of these came to operation, still clinically, one could not class them under any other diagnostic group. Of these, 27 were high and 12 were seen during the acute attacks, the bilirubin reaching as high as 2.4 units (12 mg.). During the acute attacks, the urobilinogen in the urine was always high.

The increased blood bilirubin during these attacks served to differentiate them from other forms of abdominal colic which simulated biliary disease such as those of renal, gastric, or pelvic origin with radiations to the hepatic area, and also from tabetic crises and coronary disease.

In one instance of renal stone located in the upper pole of the right kidney, the pain simulating for years biliary colic, with radiation of the pain upward to the right shoulder, the blood bilirubin was low during the attack, so that a further search revealed the renal calculus. After its removal, the symptoms disappeared.

In another instance, a man past sixty years was suffering with severe attacks of abdominal pain in the right hypochondrium for one month. The attacks would come on daily accompanied with vomiting often requiring morphin for relief. On two occasions, he had been taken to the hospital for emergency operation but the patient refused surgery. He has lost considerable weight on account of self-imposed starvation. His blood bilirubin was normal although there was some tenderness in the right upper quadrant. Careful physical examination revealed signs of tabes and later a 4+ Wassermann reaction was reported. Subsequent gall bladder studies revealed a normally functioning gall bladder.

We must, therefore, conclude that a low blood bilirubin in the face of a clinical picture simulating acute biliary disease, calls attention to other existing lesions outside the biliary tract.

Catarrhal Jaundice. There were 18 cases in this series with maximum readings varying between 9 and 30 units (45 and 150 mg.). The pathology of catarrhal icterus can no longer be viewed in the light of a mechanical obstruction of the common duct caused by a mucus plug in the sense of Virchow. From the work of Eppinger,[5] we know that it consists of a necrosis of the liver parenchyma, analogous, in a minor degree, to acute yellow atrophy of the liver. The production of jaundice is considered as brought about by the extravasation of bile in the necrotic areas, which, in view of the

disturbed relation of the bile capillaries, becomes reabsorbed directly into the hepatic veins and carried to the general blood stream. In addition, however, some of the bile pigment which has not been worked upon by the diseased polygonal cells of the liver likewise escapes into the general blood stream and is thus responsible for the delayed or biphasic van den Bergh reaction.

In some instances of catarrhal jaundice, subacute liver atrophy, arsphenamin icterus, cardiac failure, the van den Bergh reaction may go through all stages from a completely delayed to a prompt direct reaction as the disease progresses.

Fiegel and Querner[1] also suggest that there may occur a partial obstruction in the small bile capillaries due to a cholangitis along with functional decompensation of the liver cells.

The frequent studies of the blood bilirubin in cases of jaundice, noting the progression or regression of the icterus, will help us recognize the character of the disease whether obstructive requiring surgery, or a nonsurgical toxic condition.

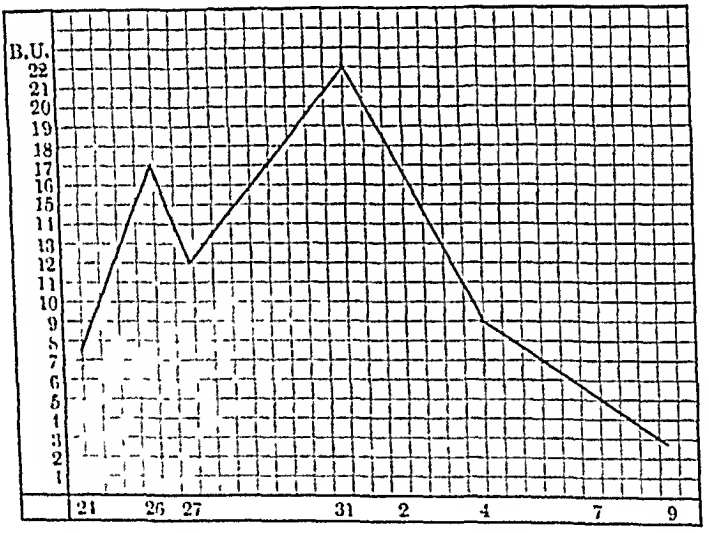

FIG. 1.—Mrs. J. F. (Sydenham Hospital). Bilirubin curve in mild case of catarrhal jaundice. Maximum 22 units (110 mg. per 1000 cc.). October 24 to November 9.

It must, however, be borne in mind, that occasionally in toxic icterus there may suddenly occur a remission of the disease and the curve rise temporarily (Fig. 1); also, that in complete obstruction associated with carcinoma of the head of the pancreas, the bilirubin may drop after a while to a lower level and there remain stationary (Fig. 2). The presence of duodenal bile is not conclusive in ruling out malignancy in and about the common duct, for in the late stage of carcinomatous growths in the head of the pancreas or in the

papilla of Vater, the growth may break down through ulcerative processes and allow bile to pass through into the duodenum. This was noted several times in proven cases of carcinoma of the head of the pancreas.

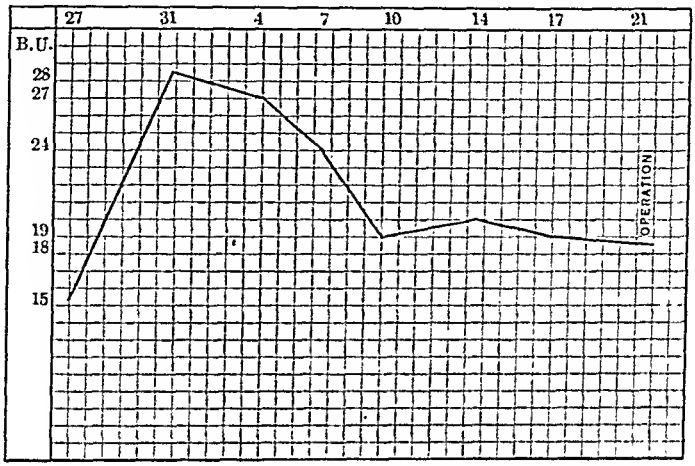

FIG. 2.—S. L. Blood bilirubin curve in case of carcinoma of the head of the pancreas. Maximum 28 units (140 mg.)—stationary 18 units (90 mg.). January 27 to February 21.

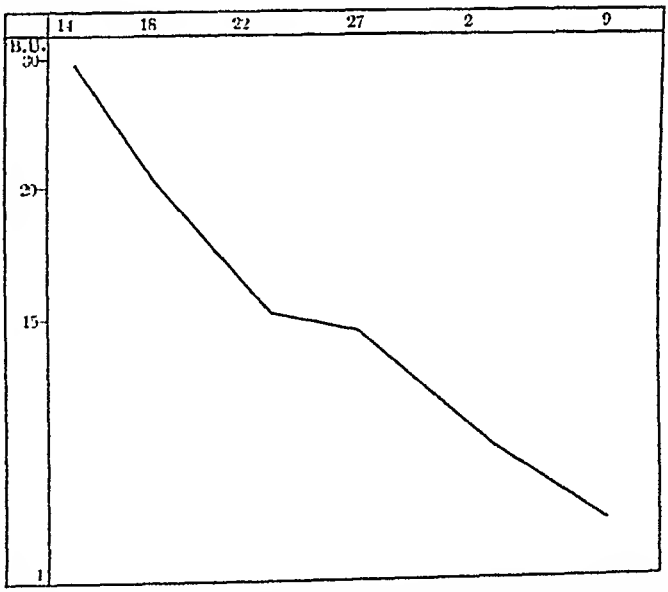

FIG. 3.—K. S. (Sydenham Hospital). Bilirubin curve in case of delayed arsphenamin jaundice. Maximum 30 units (150 mg.). August 14 to September 9.

In the differential diagnosis between the obstructive and toxic jaundice, the daily studies of urobilinogen in the urine[9] will help us far more readily to differentiate these conditions. Its presence in the urine in appreciable amounts speaks invariably for a catarrhal or toxic jaundice.

Arsphenamin Icterus. In the treatment with the arsphenamin group, it is important to study the bilirubin content of the blood before each treatment and note the effect on the liver. The arsenical should be discontinued if the bilirubin remains high. In one instance, after two treatments with neoarsphenamin a delayed reaction ensued with the developing of intense jaundice, the bilirubin reaching 45 units (225 mg.) (Fig. 3). The patient remained gravely ill for two months.

Cirrhosis of the Liver. There were 6 cases of biliary cirrhosis and 4 of atrophic cirrhosis with ascites studied. In the biliary cirrhosis group, there was always a latent state of jaundice, the bilirubin being between 2 and 4 units (10 and 20 mg.), rising at times to 9 and 12 units (45 and 60 mg.) during periods of exacerbation accompanied with pain, temperature, and jaundice. Atrophic cirrhosis with ascites showed only a moderate elevation between 1 and 1.5 units (5 and 7.5 mg.).

Carcinoma of the Liver. There was one primary (autopsy) and five metastatic carcinomata. The blood bilirubin in the early stages of carcinoma of the liver usually remains normal and does not begin to rise until interference with the flow of bile takes place. The urobilinogen in the urine may be constantly high and the bromsulphalein may also show retention, before appreciable jaundice is apparent.

Cardiac Diseases. In this group, there were 16 cases with chronic endocardial disease and 8 with symptoms of coronary disease. Of the chronic endocarditis cases, 6 had high blood bilirubin figures and were all in a state of decompensation. The figures varied from 1.25 to 3 units (6.25 to 15 mg.). All the coronary artery cases were normal. This makes an important factor for differential diagnosis between cases of severe attacks of angina pectoris and acute attacks of cholecystitis or cholelithiasis which occasionally cannot be readily differentiated. In 2 instances, diagnosis between coronary thrombosis and biliary disease offered some difficulty. There was a slight elevation of temperature and leukocytosis of 11,000 to 12,000 and in both intense precordial and epigastric pain accompanied by shock. While clinically they pointed more to a coronary lesion, the blood bilirubin, however, was high in both instances being 2 to 2.5 units (10 to 12.5 mg.) respectively. Electrocardiographic tracings were negative. The prompt recovery and the subsequent progress of the cases proved the diagnosis of biliary disease.

Blood Diseases. There were 4 cases of pernicious anemia with bilirubin figures between 2 and 3.1 units (10 to 15.6 mg.). During

the remission stage they came down to 1 unit. This was in striking contrast to the secondary anemias. In a series of 14 cases of carcinoma of the stomach, the blood bilirubin was always a low normal from 0.4 to 0.5 units (2 to 2.5 mg.). There were 10 cases of achylia gastrica with absence of free hydrochloric acid and enzymes. All had low bilirubin figures. While some were associated with anemia, the low blood bilirubin, however, pointed to its secondary nature.

There were 2 cases of purpura hemorrhagica, 3 of leukemia, (1 acute myeloblastic) in which the bilirubin figures were low. There were 2 cases of polycythemia with 1.5 and 2 units (7.5 and 10 mg.) and 1 in which pemphigus developed with a low bilirubin of 0.5 units.

Peptic Ulcer. In this group, there were 34 instances of duodenal and 6 of gastric ulcer. All the gastric-ulcer cases showed normal figures. Out of the 34 duodenal, only 5 showed slight elevation, from 1 to 1.5 units (5 to 7.5 mg.) and these were associated with gall bladder adhesions.

Chronic Appendicitis. There were 35 patients suffering with chronic appendicitis, most of whom had an acute attack at one time or another. They presented tenderness in the right iliac fossa, revealing radiographically either stasis in the appendix with tenderness under the fluroscope, or complete lack of filling of the appendix. The blood bilirubin was low in all with the exception of 3 cases in whom it was slightly above normal being 1, 1.4, and 1.25 units.

Ulcerative Colitis. In 6 cases of ulcerative colitis with typical proctoscopic pictures, the blood-bilirubin figures were all normal.

Hypertension and Nephritis. There were 15 cases of hypertension and 9 of nephritis without hypertension. In only 2 cases of hypertension were the bilirubin figures above normal: 1.35 and 1.65 units (6.75 and 8.25 mg.). The rest were normal and in the nephritis cases, they were mostly low normals.

Endocrine Disorders. There were 6 instances of hyperthyroid and 4 of hypothyroid disease, and 2 of pituitary dysfunction. All had normal blood bilirubin figures.

Diabetes. Fourteen cases of diabetes gave normal figures. In 3 of the more severe, untreated cases, the bilirubin was slightly above normal, 1.1, 1.2 and 1.4 units (5.5, 6 and 7 mg.). It is interesting that during the severer stages of diabetes, especially with ketone bodies in the urine, the urobilinogen in the urine was invariably high and disappeared promptly upon the administration of insulin.

Ten cases of pulmonary tuberculosis, 5 cases of bronchial asthma and 3 cases of epilepsy, all gave normal figures.

Summary. 1. The blood bilirubin estimation gives us most information in the latent state of icterus before evidence of clinical jaundice has appeared. In a routine examination of chronic ambulatory patients with symptoms of digestive and nervous disturbances a group of 29 cases have been found to give evidence of hepatic

derangement, as indicated by the high blood bilirubin corresponding to the latent icteric stage. This group represents a clinical entity which might be designated as hepatic toxemia, the result of a toxic hepatitis. The possibility of regarding this condition as a precursor of the chronic hepatic cirrhosis is to be considered.

2. Thirty-eight cases of cephalic and abdominal migraine were found to give high bilirubin readings in the latent stage, pointing to hepatic dysfunction as a contributory factor in this disorder.

3. In the large group of cholelithiasis and cholecystitis, the test is only of value during the acute biliary attack when it serves to differentiate it from other forms of abdominal colic, including tabetic crises and angina pectoris.

4. Repeated blood studies in jaundice, noting the course of the bilirubin curve will help differentiate an obstructive from a catarrhal or toxic jaundice.

5. In the group treated with arsphenamin, it is important to watch the bilirubin curve in order to avoid arsenical liver toxemia.

6. Cardiac disease gave high readings only during the stage of decompensation with engorgement of the liver.

7. High blood-bilirubin readings are found in pernicious anemia, distinguishing it from all forms of secondary anemia. Achylia gastrica, carcinoma of the stomach, the leukemias, purpura hemorrhagica, all give low figures.

8. Peptic ulcer, chronic appendicitis, intestinal stasis, ulcerative colitis, pulmonary tuberculosis, asthma, hypertension, nephritis, and endocrine disease in the main give normal readings.

9. In carcinoma of the liver, higher readings are only obtained when there is a direct interference with the flow of bile by compression of the intermediary or larger ducts.

10. The van den Bergh method has the advantage of being uninfluenced by carotinemia and hemolysis and also differentiates the type of jaundice by its different reactions. In deep jaundice the modified van den Bergh should be used.

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THE HEREDITARY FACTOR IN ALLERGIC DISEASES.*

With Special Reference to the General Health and Mental Activity of Allergic Patients.

By Ray M. Balyeat, M.A., M.D., F.A.C.P.,
OKLAHOMA CITY, OKLA.

The apparent apathy of American clinicians in regard to the problem of inheritance in medicine is amazing. Many physicians recognize the importance of a study of the hereditary factor in some of the rare conditions, for example, hemophilia, but few consider that the application of modern genetic methods is of practical value in the solution of many clinical problems. The increase in the number of articles on the clinical significance of heredity, however, will have its effect in removing this temporary blindness. Surely full and free recognition of the specific family traits would be of assistance to any physician in his diagnosis and therapeutics. The paucity of literature concerning the clinical importance of the study of the hereditary factor in allergic diseases has encouraged the writer to further his study and writing on the subject. In this paper will also be presented some observations concerning the general health and the mental activity of allergic patients.

Age of Onset of Clinical Manifestations of Allergy.

In a recent work on the acquisition of human hypersensitiveness, the writer[1] studied the influence of the hereditary factor in a group of 1000 cases of atopy (hay fever and asthma). It was found that 58.6 per cent of all cases with a bilateral family history manifested clinical symptoms of specific hypersensitiveness in the first decade. There were 32.3 per cent with a unilateral history that developed clinical symptoms within the first ten years of life. In only 3 cases with a bilateral family history was the onset after thirty years of age. In 30.8 per cent of the unilateral cases symptoms developed between the ages of twenty and thirty years, which is in marked contrast to 10 per cent of those with a bilateral family history that manifested symptoms during this same period. Our findings, therefore, indicate that inheritance is the chief factor in determining whether an individual will ever develop clinical manifestations of hay fever or asthma, and governs to some extent the time in life when symptoms will appear.

* Read before the American Association for the Study of Allergy, at Minneapolis, Minn., on June 11, 1928.

Terms "Atopen" and "Protein" are Used Interchangeably.

In this paper, as in the previous study, the term "atopen" and "protein" will be used interchangeably. "Atopen" is a term suggested by Coca and Cooke[2] to designate the substance to which patients become specifically sensitive. The term "atopy" will be used, and was also suggested by the same authors, to designate inherited human hypersensitiveness.

Multiple Sensitivity is the Rule.

Our records showed that 21 per cent of all cases that developed clinical manifestations of atopy in the first decade gave clinical and cutaneous evidence of a sensitivity to more than two groups of atopens. In other words, a child born into the world with the ability to become sensitive to one group of proteins should, and in most cases actually does, become sensitive to other groups.

Influence of Protein Contact.

In this work, attention was also called to the fact that the degree of protein contact has much to do with determining the individual protein or groups of protein to which a patient may become specifically sensitive. For example, Peshkin,[3] in a study of 100 asthmatic children from Jewish families who sleep on rabbit hair mattresses, found 49 per cent sensitive to rabbit hair, while in a similar series we found 43 per cent sensitive to feathers and only 2 per cent to rabbit hair. An individual working in a flour mill, if born with the ability to become sensitive, will probably develop a specific sensitivity to wheat flour, while a rancher will become specifically sensitive to cattle hair. We find a large per cent of our hay fever and asthma patients who come from the Russian thistle district of our state sensitive to Russian thistle pollen. It may be concluded, therefore, that the extent to which an individual is exposed to any given atopen largely determines whether or not a sensitivity to that particular atopen will develop.

Results of Protein Tests on the Newborn.

Protein tests on 119 newborn were done as a means of substantiating or disproving the correctness of our clinical evidence that a child may be born specifically sensitive. These children were all tested before they were three days old and the majority on the first or second day. The food proteins used were eggs, milk and wheat. We found reactions easy to read inasmuch as the skin of infants reacts very slightly to trauma from the scalpel compared with the same amount of trauma on the skin of adults. One child showed a 4+ reaction to wheat, which lasted one hour and ten minutes.

Another gave an unquestionable 3+ reaction to egg protein, which persisted for fifty minutes. Both reactions proved positive on repeating the test.

Possibilities of Specific Sensitivity Developing in Utero.

Physiologists, chemists and immunologists tell us that during embryonic life food products, bacteria and antibodies from the blood of the mother enter the arterial system of the child with practically no change. Therefore, if heredity predetermines whether or not a child is to become specifically sensitive, which is Coca's[1] idea and appears to be true from our own findings and those of Cooke and Spain,[5] then we must conclude that during embryonic life a child with the inherent ability should, in some cases, acquire a specific sensitivity to food protein, or a nonnitrogenous product associated with the protein while *in utero*, and therefore, be born specifically sensitive. Several reports of cases showing clinical evidence that a patient may be born specifically sensitive were given, which along with the experimental evidence may help to answer the frequent question of the pediatrician concerning the time children develop a specific sensitivity.

Atopic Bodies May or May Not be Protein.

Throughout the work just mentioned, it was pointed out that it has not been definitely proved that the substance to which patients become specifically sensitive is always protein. In fact, Grove and Coca,[6] and also Black and Moore,[7] have shown experimentally that the product to which patients become specifically sensitive is frequently not protein. The physiologic chemists tell us that before the proteins are absorbed by the intestinal tract into the blood stream they are hydrolized to amino acids and are absorbed as such and circulate in the blood stream in that form. Prof. Howard B. Lewis,[8] of the University of Michigan, believes that protein is not absorbed through the intestinal tract in any other way. Walzer,[9] however, has recently demonstrated that unaltered protein of at least the part of the egg to which the patient is sensitive could be frequently passed unchanged into the blood stream.

The author has observed clinically that the atopic substance in food, whether it be protein or nonprotein in character, probably is absorbed by the mucous membranes of the mouth and stomach, as symptoms of a specific sensitivity will frequently appear from two to ten minutes after the patient eats the protein to which he is specifically sensitive, which is not sufficient time for the digestion of proteins to take place. After considering our observation of the clinical manifestations of atopy in the light of the present knowledge of the chemistry of digestion and the normal constituents of human and

cows' milk, we were led to believe that the substance to which patients become sensitive, in many cases, is a nonnitrogenous one.

Family History of Allergy in the Normal.

In a study just completed of 1117 normal university students, it was found that a positive family history of hay fever and asthma occurred in relatives of the first degree only in 8.3 per cent, which is in marked contrast to such a history found in 60.1 per cent of patients suffering with hay fever or asthma.

Clinical Evidence that Patients are Born Specifically Sensitive.

One hundred and eighty children with hay fever and asthma, in all of whom the hypersensitive condition was demonstrated by a positive intradermal test, are now being presented with an idea of offering additional evidence that a child may be born specifically sensitive. Of the 180 children, 24, or 13 per cent, developed symptoms during the first year. Of the 24, only 2 were found not sensitive to food. Three cases developed symptoms the first day they were born, and 8 cases manifested evidence of specific sensitivity while they were nursing the mother's breast, before supplemental feeding was given. Four developed allergic symptoms as soon as cream of wheat was added to the diet. Two children developed evidence of specific sensitivity on the addition of eggs to their diet. All except 2 of the 24 cases who were sensitive to food were also sensitive to inhalant proteins. Clinically, from the evidence just given, it appears that some of these cases were specifically sensitive at birth.

Specific Sensitivity not Inherited.

Neither in our previous study nor in the present is there any evidence that the specific sensitivity is inherited, but the ability to become so is inherited. The type of sensitivity the antecedent suffered from has no relation to the type the descendant may have. For example, a father may have hay fever due to a specific sensitivity to Russian thistle and his son eczema due to a sensitivity to eggs, and yet their ability to develop their individual specific sensitivity to different atopens came from the same germ plasm. It must be remembered that we do not inherit from our parents or grandparents or from any one, so far as that is concerned. Our parents and we inherit from the same germ plasm and, therefore, the same plans and specifications are used in our make-up, which accounts for our having traits in common. I am the father of my son, legally, though biologically he is a younger brother by a different mother. We inherit germ cells whose chemical composition is similar. In these germ cells are determiners which decide whether

or not we will have the ability to become specifically sensitive, but we do not inherit the specific state. With this ability we may become sensitive to any atopen with which we have adequate contact.

Mendel's Law Followed.

In an unpublished paper by the writer, good evidence is offered to show that the transmission of the ability to become specifically sensitive follows Mendel's law and that the nature of the inheritance is as a single dominant factor. From the evidence which we have, it appears that in the linkage, eczema and migraine are interchangeable with hay fever and asthma. Adkinson,[10] in 1920, published some data from which she drew conclusions that the nature of the inheritance was as a recessive factor. However, if this were true all of the children with a bilateral family inheritance should show traits of allergic conditions, whereas it does not actually happen. Cooke and Vander Veer[11] believe that the nature of the inheritance is as a single dominant factor but suggest that it might be multiple. From our evidence, it appears that it is single and dominant.

The Relation between Asthma, Hay Fever, Eczema and Migraine.

Three family trees are offered to show the relation between asthma, hay fever, eczema and migraine.

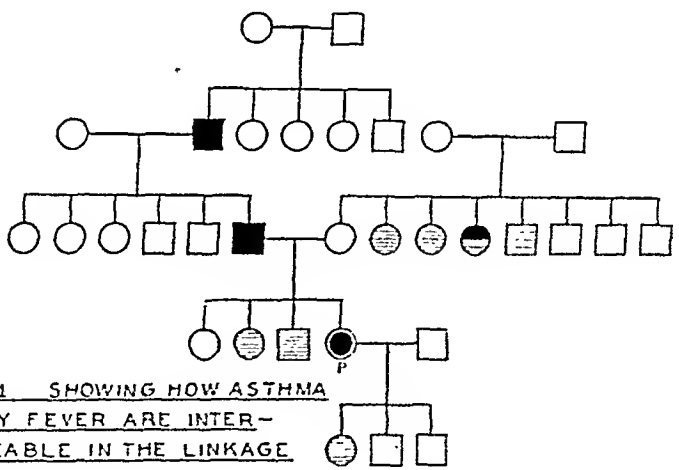


CHART 1 SHOWING HOW ASTHMA AND HAY FEVER ARE INTER-CHANGEABLE IN THE LINKAGE

In the pedigree as shown in Chart 1, one will note that the grandmother gave birth to three daughters and three sons, only one of whom developed an allergic condition, this being a daughter. This daughter married a man who did not manifest any form of allergy. There were three sons and one daughter born, and of the four, one

son had hay fever, the daughter had hay fever, and the other son had asthma. This asthmatic son mated with a woman without allergic symptoms. From the union, we find two daughters and one son, of whom only the son showed evidence of allergic symptoms, which were manifested in the form of hay fever. It is also noted that on the grandfather's side of the family there were two uncles with hay fever, one with hay fever and asthma, and an aunt with hay fever. There is a possibility that the paternal grandfather, inheriting from the same germ plasm that his brothers and sisters did, might have developed allergic symptoms if he had lived longer, but he died young. From the ancestral tree, it certainly appears that asthma and hay fever are interchangeable in the linkage.

In Chart 2, we find a patient whose father and mother both had migraine and whose paternal grandmother and maternal grandfather

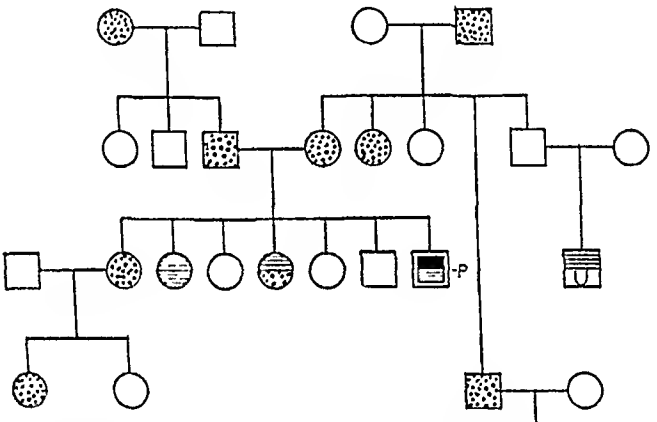


CHART 2 SHOWING HOW MIGRAINE AND URTICARIA ARE INTER-CHANGEABLE WITH ASTHMA AND HAY FEVER IN THE LINKAGE

also had migraine. This patient has five brothers and one sister, of whom one brother has seasonal hay fever, one brother has perennial hay fever and migraine, and one brother has migraine. One brother is married and his wife has no allergic symptoms. From this union we find two males, one of whom has migraine. The patient who is an asthma and hay fever sufferer has one paternal uncle with migraine and one paternal aunt with migraine. The paternal aunt with migraine has a daughter without allergic symptoms, but she is a child and has lots of time yet for symptoms to appear. One paternal aunt has no symptoms, but she has a daughter with seasonal hay fever and hives. This aunt is still a young woman and has plenty of time for allergic symptoms to appear, which would complete the chain. It will be noted that the migraine grandparents produced children with migraine and these children produced hay

fever, migraine, urticaria, eczema and asthma in their children. From this pedigree, and from many other similar cases, we are led to conclude that asthma, hay fever, migraine and urticaria are interchangeable in the linkage.

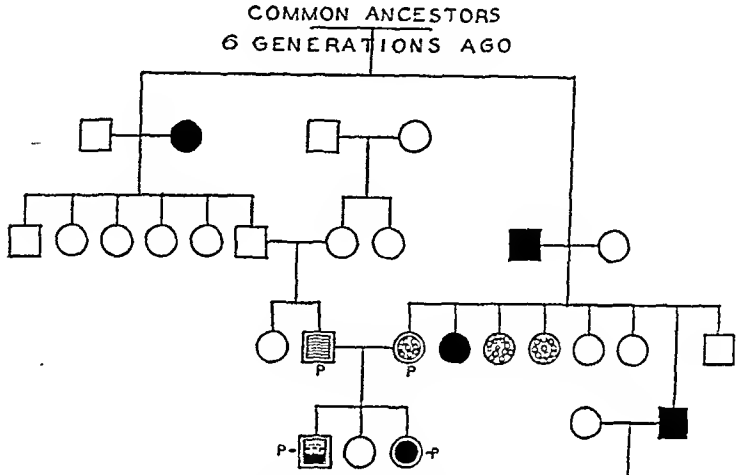
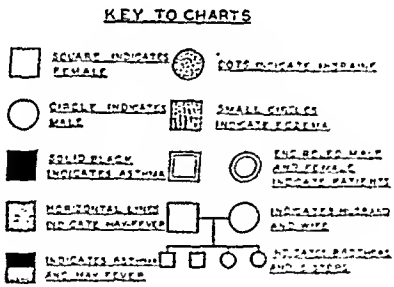


CHART 3 SHOWING HOW HAY FEVER AND ECZEMA ARE INTERCHANGEABLE IN THE LINKAGE



This case is an interesting one since from the history we find that our patients come from common ancestors six generations ago. The patients are four in number, a father with eczema, a mother with seasonal hay fever, and from this union came three children, one with seasonal hay fever, eczema and asthma, and another, asthma. The third child, a boy, died of diabetes when an infant. The father of the two children who are patients had a brother with asthma, two brothers with eczema, and a sister with asthma, and this sister gave birth to two boys with eczema. The mother of the father was an asthmatic. The grandfather of the mother of our two children who

are patients, had asthma, but we can find no history in the mother or the father of the mother of our two allergic children. However, this mother without symptoms might have developed symptoms if she had lived longer, as we have seen patients who developed typical allergic symptoms as late as seventy-five years of age. The allergy in this family is being transmitted from both sides, and they gave a definite history of being relatives, knowing that they are from the same grandfather six generations ago. From this tree, and others which we have, we are led to believe that asthma, hay fever and eczema are interchangeable in the linkage.

If asthma, hay fever and certain forms of eczema, hives and migraine, are interchangeable in the linkage, it is good evidence that they have a common cause.

The Rôle Played by Heredity in Determining the General Health of Allergic Patients.

In our study of allergic patients during the past nine years, we have not only been impressed with the importance of the hereditary factor in determining whether or not an individual will ever develop hay fever or asthma but also with the rôle played by heredity in determining the general health of the individual. Our[12] observations have led us to believe that allergic patients develop a general resistance to infectious diseases which is far above the normal. On eliciting the past history, the question "You have been sick a great deal, have you not?" is routinely asked. Answers such as "I have never been sick," or "Doctor, I am disgustingly healthy other than my asthma and hay fever," are those given by a large percentage of adult patients. When parents are asked concerning the past history of their child, they commonly tell us that the child has been sick a great deal, but on close questioning one finds that other than hay fever or asthma or some allied condition, namely, eczema, urticaria or migraine, they have been unusually well.

As a means of proving or disproving the correctness of this impression that allergic patients are far above the average in general health, we have made a careful study of the histories of 1217 patients with hay fever, asthma and allied conditions. Of this number 532 were adults and 34 were children suffering from seasonal hay fever. There were 372 cases of asthma in adults and 174 asthmatic children. Perennial hay fever was found in 49 adults and 6 children. There were 31 adults and 19 children suffering from eczema, hives or migraine, who had no symptoms of asthma or hay fever. The patients studied have been classified according to health as "above normal," "average normal," and "below normal." Those placed in the classification "above normal" were cases that answered the question "You have been sick a great deal, have you not?" by saying that they had never been sick. Of course, patients answer-

ing the question in such a manner would frequently modify it a little, but the diseases of childhood or any disease that they would have during adult life would usually be very mild. Or in this class, if it was a child, one would elicit from the mother or father a history of but few of the contagious diseases. Under the classification "average normal" were listed the cases, both adults and children, who had had the average number of diseases of childhood with moderate severity and some of the diseases which usually occur in adult life. Under the classification "below normal" were placed those patients who had had a larger number of the contagious and infectious diseases than usual or who were far below weight for some unknown reason and in general somewhat delicate.

Of the 532 seasonal hay fever cases in adults, 420, or 78.9 per cent, were classified as above normal, 84, or 15.7 per cent, normal, and 28, or 5.2 per cent, below normal. Of the 34 children suffering with the same disease, 32, or 94.1 per cent, were classed above normal, and 2, or 5.9 per cent, normal. There were none below normal.

Of the 372 cases of asthma in adults, 260, or 69.8 per cent, fell in the above normal class, 73, or 19.6 per cent, in the normal, and 39, or 10.4 per cent, in the classification below normal. Of the 174 children suffering from asthma, 126, or 72.4 per cent, fell in the classification above normal, 40, or 22.9 per cent fell in the average normal, and 9, or 4.6 per cent, in the below normal.

TABLE I.—SUMMARY OF GENERAL HEALTH OF ALLERGIC PATIENTS.

	Above normal.		Normal.		Below normal.	
	Number of patients.	Per cent of total.	Number of patients.	Per cent of total.	Number of patients.	Per cent of total.
Seasonal hay fever in adults	420	78.9	84	15.7	28	5 2
Seasonal hay fever in children	32	94.1	2	5.9	None	
Perennial hay fever in adults	30	61.2	11	22.4	8	16 3
Perennial hay fever in children	3	50.0	2	33.3	1	16.6
Asthma in adults	260	69.8	73	19.6	39	10 4
Asthma in children	126	72.4	40	22.9	8	4.6
Allergic eczema, hives and migraine in adults	24	77.4	5	16.1	2	6 4
Allergic eczema, hives and migraine in children	17	89.5	None	...	2	10 5
Total number of allergic cases seen	912	74.9	217	17.8	88	7 2

There were 49 adult cases of perennial hay fever, 30, or 61.2 per cent, of which were above normal, 11, or 22.4 per cent, normal, and 8, or 16.3 per cent, below normal. There were 6 children with perennial hay fever, 3, or 50 per cent, above normal, 2, or 33.3 per cent, average normal, and 1, or 16.6 per cent, below normal.

Of the 31 adult cases suffering from hives, eczema or migraine, 24, or 77.4 per cent, were above normal in health, 5, or 16.1 per cent, average normal, and 2, or 6.4 per cent, below normal. Of the 19 children, 17, or 89.5 per cent, were above normal, and 2, or 10.5 per cent, below normal.

From the foregoing considerations, we are led to the conclusion that our impression concerning the general health of allergic patients is correct. An answer to the question as to why a hay fever patient or one suffering from some other form of allergy, should have a superior resistance against infectious diseases is not easy. The writer wishes to offer the following explanation as a possible answer. An individual who inherits the ability to become specifically sensitive to cat hair, orris root, pollen, food protein or some other atopen, certainly has a body that is made up of cells which are hyperirritable or hyperactive compared with the normal, since in many cases the atopic bodies are formed on first contact with the atopen. It is true that the formation of antibodies and atopic bodies is two separate and distinct processes; however, they are similar in nature. If this be true, it would be logical, then, to believe that an individual whose cells develop atopic bodies with ease should also develop antibodies against pathogenic organisms with similar ease. Therefore, an allergic child should, early in life, develop a larger number of specific antibodies against pathogenic organisms than will a nonallergic one, thereby giving him greater resistance against diseases in general. Allergic patients, therefore, would be above normal in general health, and it appears that they are.

It has been the author's experience, and likewise true of other allergists and also phthisiologists, that it is very unusual to find an open case of tuberculosis in a patient whose allergic symptoms appeared in the first or even in the second decade. The cause for the striking absence has been attributed to the chronic congestion of the lungs produced by asthma. However, this absence is almost as striking in hay fever and eczema as it is in asthma. In asthma cases no doubt the congestion is one factor, and may be the only factor in preventing the tuberculous infection from becoming an open case of tuberculosis. However, the inherent ability of the patient to produce a larger number than normal of antibodies against the tubercle bacilli may play a definite part. In allergic cases other than asthma the first factor mentioned is absent, which leads us to believe that the latter factor plays a very important rôle in protecting the allergic cases, other than asthma, against tuberculosis.

A knowledge of the above findings may be of importance from a practical standpoint, since many physicians in examining such patients do much unnecessary Roentgen raying of the teeth, sinuses and chest. They also frequently spend a great deal of unfruitful time and energy in various types of laboratory work trying to find

the cause of the asthmatic symptoms. Needless surgery is often done. A careful detailed history of an asthmatic or hay fever case will usually tell one whether or not the patient requires laboratory study other than testing for the specific sensitivity. The fact that 74.9 per cent of all the allergic cases seen by us were far above normal except for their allergic condition is fair evidence that at least three-fourths of the allergic patients who come seeking relief from their trouble, do not need a great deal of laboratory investigation except for careful testing and retesting for the proteins to which they are specifically sensitive.

From general observations by some of our leading students of neuropsychiatry it appears that hay fever and asthma are uncommon in the insane. Recently the writer visited one of the Oklahoma insane hospitals and in going over the subject of asthma and hay fever in the insane with the assistant superintendent he told me that he could think of no case in the institution who was suffering from periodic attacks of asthma. In this institution, there are about 1000 cases. This led us to investigate the question more fully. Dr. D. W. Griffin,[13] superintendent of the Oklahoma State Hospital, reports a total of 8 cases suffering from periodic attacks of dyspnea out of a total of 1670 patients. Four of these were over fifty years of age, and the physicians in charge thought that some or all of these cases were cardiorenal in type. Assuming that 2 of the 4 cases reported were true asthma, then 6, or less than one-third of 1 per cent of the patients in the Oklahoma State Hospital suffer from asthma.

Dr. William A. White,[14] of Saint Elizabeth's Hospital, Washington, D. C., was prevented from answering the questionnaire sent him concerning the number of cases of asthma in his institution by lack of time, but in answer to the question concerning hay fever, he states: "I am informed by the doctor in charge of the medical and surgical department that so far as he can recollect only 2 cases of typical hay fever were seen in those departments during the summer and it is his impression that the condition is relatively strikingly absent in our patient population of 4000."

Hay fever and asthma patients are less likely to become insane than the normal individual probably due to the fact that their blood stream contains a greater number of specific antibodies against the various pathogenic organisms that invade the body, such as the Treponema pallidum, the organism that causes encephalitis lethargica, and others. It does not seem reasonable that there would be anything in their physiochemical makeup to protect them against the type of insanity which is inherited.

Mental Activity of Allergic Patients.

In taking histories of asthmatic children, we have been impressed with the fact that in spite of their being out of school one-third to

three-fourths of the time, due to asthmatic attacks, they have passed their grades with ease. On inquiry, we find their records as students much superior to the average child. We thought it might be of interest to make a study of the mental activity of these children. A list of our asthmatic children who live in Oklahoma City, on whom a hypersensitive condition was demonstrated by a positive intradermal test, was given to the Oklahoma City school statistician. These children ranged in age from six to twelve years. The statistician reported the intelligence quotient on 40 of these patients. On the remainder, it had not been determined. He also reported to us the intelligence quotient on 40 students chosen consecutively from two schools in the better sections of the city. The Otis self-administering test of mental ability was the one used in determining the intelligence quotient on the 80 students studied. The classification used is Dr. Terman's, the one generally accepted for this work, and is as follows:

Below normal	70 to 90
Normal	90 to 110
Superior	110 to 120
Very superior	120 to 140
Near genius	140+

Following are the results of the tests as reported on the asthma and hay fever patients. Of the 40 cases, 12, or 30 per cent, fell in the normal class; 12, or 30 per cent, in the superior; 15, or 37.5 per cent, in the very superior class; and 1, or 2.5 per cent, in the classification which Dr. Terman designates as near genius.

The following report was given on the 40 consecutive nonallergic students. Of these 40, 2, or 5 per cent, were below normal; 32, or 80 per cent, fell in the normal group; 4, or 10 per cent, in the superior group; and only 2, or 5 per cent, in the very superior.

TABLE II.—SUMMARY OF INTELLIGENCE QUOTIENT ON 40 ALLERGIC AND 40 NONALLERGIC STUDENTS.

	Allergic.	Nonallergic.
Below normal:		
Number of students	None	2
Per cent of total	..	5.0
Normal:		
Number of students	12	32
Per cent of total	30.0	80.0
Superior:		
Number of students	12	4
Per cent of total	30.0	10.0
Very superior:		
Number of students	15	2
Per cent of total	37.5	5.0
Near genius:		
Number of students	1	None
Per cent of total	2.5	

It is of interest to note that 37.5 per cent of the allergic students fell in the classification "very superior," while only 5 per cent of the nonallergic students fell in that class. Of the allergic students, there were none below normal and only 30 per cent fell in the normal class, which is in marked contrast to 80 per cent of the nonallergic students that fell in the normal group. These figures, without question, are striking, and we are unable to explain the cause. In some physical disabilities, such as deformities of various parts of the body, patients spend a great deal of time in study and, therefore, are mentally very alert but this does not hold true for the asthmatic patient. When they are sick they are too sick to study, and when they are well they are as normal as any other child.

Orthopedic surgeons frequently spend years in correcting deformities due to nerve and bone pathology, and the correction is usually only in part. Cardiologists are doing some wonderful and worthy work both in children and adults who have suffered from valve and muscle lesion, by training them how to protect their hearts. The urologist does much to lengthen the life of chronic nephritics by patiently guiding them over a period of years. A careful study of the mentally deficient child, and the adult whose nervous system is inefficient, is worth while.

Many orthopedic, and a large percent of the chronic cardiac, nephritic and mental cases, will always be far below par in spite of the efforts of the skilled surgeon and physician, yet treatment over a period of years, if necessary for even partial relief, is justified. Today, with few exceptions, results in the treatment of hay fever and asthma is more satisfactory than the treatment of any other chronic disease. Protecting the hay fever patients from their symptoms is frequently the prevention of asthma. An asthmatic relieved of symptoms, differing from patients suffering from other chronic diseases, is usually above normal both physically and mentally. Therefore, if the treatment of the other chronic diseases is worth while, and it is, although the outlook is frequently not bright, how much more are we justified in a careful study and treatment of the asthma and hay fever patient, over a period of years if necessay, for relief or cure.

Conclusions. 1. Inheritance appears to be the chief factor in determining whether or not an individual will ever develop hay fever or asthma, and to some extent governs the time in life when symptoms may appear.

2. The earlier in life an individual becomes sensitive, the greater the tendency to develop a sensitivity to more than one group of proteins.

3. The extent to which an individual is exposed to any given protein has much to do with determining whether or not a sensitivity to that particular protein will develop.

4. The substance to which patients become specifically sensitive, chemically and clinically, in many cases, is a nonnitrogenous one.

5. Clinically, the substance, whether protein or nonprotein, to which patients become specifically sensitive, may be found in cow's milk and breast milk.

6. A child may be born specifically sensitive to a food protein or a substance closely associated with it.

7. The ability to become sensitive is transmitted from one generation to another, but not the specific state.

8. The character of the inheritance is as a single dominant one.

9. It appears that in the linkage, eczema and migraine are interchangeable with hay fever and asthma.

10. Allergic patients develop a general resistance to infectious disease which is far above the normal.

11. A careful detailed history will usually determine whether an asthma or hay fever patient has complications that need investigation other than tests for a specific sensitivity.

12. Allergic patients whose symptoms manifest themselves within the first or second decade seldom develop tuberculosis.

13. Hay fever and asthma are comparatively absent in the insane.

14. From our findings it appears that allergic students may be far above the normal in intelligence.

15. There is a cause for the apparent overenthusiasm of physicians who deal in allergy as a specialty.

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THE INCIDENCE OF INTRACRANIAL TUMORS WITHOUT "CHOKED DISK" IN ONE YEAR'S SERIES OF CASES.*

By William P. Van Wagenen, M.D.,
INSTRUCTOR IN SURGERY UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY, ROCHESTER, N. Y.

(From the Surgical Clinic of the Peter Bent Brigham Hospital, Boston, Mass.)

During my year's period (October, 1924, to November, 1925) in charge of the neurosurgical patients on Dr. Cushing's service, I was impressed by the number of patients entering the clinic with a complete absence of choked disk, even though many of them had otherwise an unmistakable brain tumor syndrome. One of my earliest experiences of this nature was with a comatose patient who died a few hours after admission, even before a diagnosis could be made, much less an operation performed. The examination of the eyegrounds showed them to be entirely normal, yet the autopsy disclosed a large temporal lobe tumor. The matter from the outset so surprised me that it was felt it might be of interest to report these cases, for others may labor as I originally did under the impression that tumor diagnoses are rarely made in the absence of the textbook triad of headache, vomiting and choked disk, more particularly the latter.

Of the series of 145 intracranial tumors which were verified in those twelve months by operation or autopsy, there were 17, 11.7 per cent, in which the diagnosis of tumor was made in spite of the fact that the ophthalmoscope revealed no significant change in the eyegrounds. This is, of course, excluding from the list, the adenomas of the pituitary, congenital cysts and suprasellar meningiomas, 36 in all, which are but rarely associated with choked disk. Normal fundi were also observed in 9 out of 81 cases (11.9 per cent) from among the group of tumors in which the lesion was not histologically verified, though there were trustworthy evidences of its presence shown by calcification in roentgenograms, visual field defects, distortion of the ventricles, resistance to the exploring brain needle, and so forth.

The major subdivisions of intracranial tumors used in the clinic and the reasons for employing them, as already pointed out by two of my predecessors, Dr. Percival Bailey[1] and Dr. Charles E. Locke, Jr.,[2] are three: (*a*) brain tumors verified; (*b*) brain tumors unverified; (*c*)

* Since this article was submitted for publication, a paper on the same theme (Tumeurs cérébrales sans papille de stase) has been published in the Journal de Neurologie et Psychiatrie, December, 1927, 27, 756.

brain tumor suspects. A tabulation of the year's series of cases on this basis follows:

TABLE I.—CASES ADMITTED OCTOBER, 1924, TO OCTOBER, 1925.

A. Brain tumors verified		183
(*a*) At operation	139	
(*b*) At necropsy	6	
(*c*) Re-entry and reverified	16	
(*d*) Re-entry not reverified	22	
B. Brain tumors unverified		81
(*a*) Operated upon	39	
(*b*) Not operated upon	42	
C. Brain tumor suspects		101
(*a*) Operated upon	24	
(*b*) Not operated upon	77	
Total cases admitted for question of brain tumor		365

Many of these 365 cases, to be sure, represented conditions in which there was no reason to expect a choked disk. This is particularly true of that group—the tumor suspects—which were either proven to be due to a lesion other than tumor, or so regarded. There were 3 cases of subdural hematoma, an intracranial aneurysm of the internal carotid, an abscess or two and the usual proportion of examples of cisternal arachnoiditis, or encephalitis, and of cerebral arteriosclerosis with a syndrome closely resembling tumor. Indeed not a few of these cases showed a choked disk, one of the main reasons which led to the patient's admission. But it was not so much the presence of a choked disk in these examples of pseudotumor, as the absence of this cardinal symptom in the verified or unquestioned tumor cases that caused surprise and aroused my interest.

The types and situation of these 145 verified lesions are shown in Table II.

TABLE II.

Location of tumors.	Glioma	Adenoma	Meningioma	Congenital cyst	Neurinoma	Metastatic carcinoma.	Heterotopia	Pinealoma	
Frontal	11	0	3	0	0	0	0	0	
Paracentral	2	0	3	0	0	0	0	0	
Parietal	11	0	4	0	0	1	0	0	
Supramarginal	5	0	1	0	0	0	0	0	
Temporal	15	0	0	0	0	1	0	0	
Occipital	1	0	0	0	0	1	0	0	
Pituitary	0	26	0	0	0	0	0	0	
Suprasellar	0	0	1	6	0	0	0	0	
Cerebellar	31	0	0	0	0	1	1	1	
Extracerebellar	0	0	0	0	11	0	0	0	
Optic chiasm	1	0	0	0	0	0	0	0	
Pons and basal nuclei	1	0	0	0	0	0	0	0	
Lateral ventricle	2	0	1	0	0	0	0	0	
Total	80	26	16	6	11	4	1	1	145

Literature. The presentation for treatment of an increasing number of cases of brain tumor without choked disk can well be taken as an encouraging and hopeful sign of the more widespread knowledge of this malady. For years after von Graefe[3] (1860)

demonstrated with the "mirror" the changes in the eyegrounds in cases of brain tumor, clinicians were very loath to make that diagnosis in its absence. Allbutt,[4] however, recognized that such instances did occur and observed them clinically and at autopsy. He believed that tumors of the striate bodies and thalami were not apt to produce choked disk. Jackson[5] likewise was aware that tumors did occur without ocular manifestations in spite of his statement that "optic neuritis has in my experience, almost invariably occurred with obvious local and gross changes inside the head." In an earlier contribution[6] he refers to 3 cases without choked disk: one in a man whose tumor symptoms dated back nine years and who only shortly before death developed choked disks, a second in association with a cerebellar tumor, and a third in a case of cerebellar abscess. MacDonald,[7] in 1890, reported as a rarity an autopsy of a woman, aged eighty-nine years, which revealed what was undoubtedly a large meningioma, displacing nearly two-thirds of the contents of the left cerebellar fossa. There had never been any evidence of pressure symptoms or disturbance of vision while under observation in an asylum for twenty-four years. Examinations of the eyegrounds are not reported, however. As late as 1915, Sattler[8] remarked on "double papilledema, optic neuritis, the clinical constant of brain and cerebellar tumors." Beerman's[9] report, in 1913, of 6 verified cases of brain tumor without choked disk gives the first recent hint that choked disk is constantly being looked upon as one of the later symptoms in this disease. Elsberg,[10] in 1923, puts this opinion into words and states that more and more cases of intracranial tumor are coming to operation without or with but slight papilledema. It is a relatively late symptom of expanding intracranial lesions. André-Thomas,[11] in 1921, referring, I am inclined to believe, to all cerebral tumors including those of the pituitary and Rathke's pouch which but rarely produce choked disk, states that 10 to 20 per cent may fail to show it. Paton[12] analyzed 200 verified cases of brain tumor and found that 20 per cent had normal fundi either at the time of death or operation. In a series of 60 cases Brain[13] found the percentage of normal fundi to be 21.6.

The average duration of symptoms of brain tumor prior to hospital entry in the 26 cases here reported was twenty-eight months; the longest case history was of one hundred and fifty-four months, and the shortest of one month. The average for verified and unverified cases is the same.

The phenomenon of a "foreign body" mass within the cranium giving rise to changes in the optic nerve head has called forth a number of theories for its explanation. Von Graefe[3] (1860) originally associated brain tumor with choked disk and termed the changes in the nerve head "stauungspapille." Allbutt's translation of this was "choked disk." Parsons[12] has proposed the name "papilledema." Von Graefe first proposed to explain disk changes

associated with intracranial tumors on a mechanical basis, assuming that the changes in the nerve head were due to local vascular engorgement.

Schmidt-Rimpler,[13,14] in 1869, put forward the theory that with the rise in intracranial pressure the cerebrospinal fluid was driven down the optic nerve into the lamina cribrosa. A year later Manz[15] observed early choking of the disks and distention of the subvaginal sheath of the optic nerves described by Schwalbe (1869) when he injected fluid under pressure into the subdural space. He believed, as did also Cushing and Bordley,[16,17] that the changes were due to stasis produced by the cerebrospinal fluid under pressure in the vaginal sheath of the nerve.

Deyl,[18] Dupuy-Dutemps,[19] Merz,[20] af Schultem,[21] Judeich[22] and Gunn[23] also supported the mechanical theory as the one most adequate to explain "choked disk" though each had slightly different views regarding the means by which venous engorgement of the disk was produced. Parker[24] in 1916, Kornder[25] in 1919, and Davis[26] in 1926 have repeated and reverified the experimental work of the above workers.

Liebrecht[27,28] and Schieck[29] believed that disk changes were due to lymph stasis. Paton and Holmes[30] believe it is a combination of venous engorgement and lymph stasis. The latter authors in a careful review of the work of Leber,[31] Gowers,[32] and Elschnig[33] and others who attribute disk changes to inflammatory processes find little, if anything, to support their views.

Jackson,[5] Benedikt,[34] and others have postulated that disturbances of vasomotor innervation of retinal vessels might be the cause of disk changes. Clinical or experimental support for such a view is entirely lacking.

In general, one may say that the likelihood of a tumor being accompanied by choked disk depends primarily on its interference with cerebrospinal circulation, either by position or accompanying edema. The actual size of the tumor, while undoubtedly a factor, is secondary. That tumors of enormous size or of any size may exist for years without any evidence of pressure has been recognized by many since Jackson's[6] early report of an instance of tumor without choked disk. Actual hyperplasia of brain tissue in connection with brain tumor, noted by Spiller,[35] probably plays a minor role in the production of intracranial tension. Case XI, of the present series first operated upon nine years ago and again recently, was thought to be an example of convolutional hypertrophy in association with tumor.

The failure to find choking of the disk does not mean that increased intracranial tension may not be present. In 50 per cent of the cases here reported there was evidence of such increased tension as hydrocephalus, flattening of the convolutions, protrusion of the brain after decompressive measures or convolutional impressions in the skull

demonstrated by Roentgen ray. As observed both experimentally and clinically by Cushing, Bordley[16],[17] and others, the disposition of disks to choking varies greatly. The disks of hypermetropic eyes with their more closely woven laminæ cribrosæ, I have observed, seem much less prone to choke than others. This, however, is a disputed point (Gunn[23]).

Verified Tumors Without Choked Disk. *A. Of the Posterior Fossa.* Forty-five or over one-third of the entire list of verified tumors were subtentorial lesions.

In the series of 17 verified tumors without choked disk, 6 were located in the posterior fossa and of the following description: Cases I, II, III, acoustic neurinoma; Case IV, anomalous growth of the cerebellum; Case V, medullary tumor; Case VI, midline cerebellar tumor. A hydrocephalus was present in 3 instances (Cases I, II, and VI). The tumor in Cases IV and V obviously could not interfere with cerebrospinal circulation to any extent by reason of its size and location.

Case Reports. CASE I.—Surg. No. 23090. Acoustic Neurinoma with Hydrocephalus but Without Choked Disk. H. P. J., a woman aged sixty years, entered the clinic complaining of tinnitus in the right ear of some three years' duration followed by deafness. Occipital and vertical headache, unsteadiness of gait, numbness of the right side of the face and a slight blurring of vision had been noted for six months.

The physical examination showed partial deafness in the right ear, a corneal areflexia on the affected side and a partial facial paralysis. Nystagmus, unsteadiness of gait, and a positive Romberg were the principal cerebellar symptoms.

Examination of the fundi showed them to be normal in all respects. Roentgen ray examination of the skull did not present evidence of intracranial tension. Operation revealed a large right acoustic neurinoma, the saved fragments of which weighed 9.5 gm. There was a well-marked hydrocephalus. The postoperative course was uneventful. Two and a half years later the patient reports that she "is able to do all the house work for a family of four" and considers herself quite well.

CASE II.—Surg. No. 24873. Acoustic Neurinoma—Cystic—Lying Very Low in the Posterior Fossa. J. S. R., a male aged thirty-two years, has been one of the most instructive cases of the year's series. The history is an unusual one for an acoustic neurinoma. Over a year before entry he began to complain of a sense of constriction of the head and generalized headaches. Disturbance of gait, ataxia of the arms, nausea, and vomiting, diplopia, dysarthria, and so forth, gradually appeared. Hearing remained normal. He was seen by a group of experienced neurologists, who considered him to be suffering from multiple sclerosis. The same diagnosis was independently made at this hospital when seen in the out-door department. The disks examined numerous times in this year's interval were always normal. Roentgen rays of the skull showed moderate convolutional impression suggesting intracranial pressure.

While under continued observation the patient rapidly developed choked disks in addition to his other findings and was operated on at once.

A cerebellar exploration demonstrated a relatively small, partly cystic, right acoustic neurinoma. Hydrocephalus was marked as well as foraminal herniation.

Progress to date has been excellent. Observations on hearing three weeks after operation show that he still has nearly normal hearing on the affected side. Examination of the disks eighteen months after operation showed them again to be normal.

CASE III.—Surg. No. 23884. Acoustic Neurinoma with Intracapsular Hemorrhage. B. D., a woman aged forty-seven years, was admitted to the medical wards complaining of "stomach trouble and difficulty in walking."

The present illness began four years ago with attacks of vomiting and general malaise. Three years ago she experienced a sudden attack of whistling noise in the head, numbness of the left side of the face, deafness of that ear, and a left peripheral facial weakness. Unsteadiness of gait gradually increased, along with vertigo and vomiting attacks.

On physical examination there was noted deafness of the left ear, a facial palsy on the affected side, left corneal areflexia, and hypesthesia over the left fifth nerve distribution. There was also positive Romberg, and ataxia most marked on the left side, and nystagmus with the slow component to the left.

This patient furnished an opportunity to observe very early choking. On admission, the disks were sharply outlined and cupping was to be made out. Observed just before operation the nasal borders were hazy and elevation of 0.5 degrees was measured.

A suboccipital exploration disclosed a full cerebellum with considerable foraminal herniation. A cystic tumor in the left cerebellopontine angle was encountered which was considered to be a much degenerated acoustic neuroma from hemorrhage into its substance.

The patient has been lost track of in the routine follow-up.

CASE IV.—Surg. No. 22636. Anomalous Growth of the Right Cerebellar Tonsil. N. V. E., a girl aged nineteen years, was admitted with a complaint of "fainting attacks" and staggering gait of two years' duration. In the past history, there had been numerous illnesses from infectious fevers as follows: severe tonsillitis eight years ago recurring at intervals three and four years ago, a severe attack of influenza six years ago, scarlet fever five years ago, whooping cough four years ago, measles one year ago and pleurisy one year ago. A bilateral otitis media with complete deafness for several weeks accompanied the influenza. These furnished ample reasons for suspecting that she might be suffering from a posterior fossa chronic arachnoiditis described by Horrax.[36]

On physical examination there was noted suboccipital tenderness, marked spontaneous nystagmus, positive Romberg, considerable ataxia of the legs and slight of the arms. Reflexes were hyperactive with bilateral ankle clonus.

Examination of the eyegrounds on admission showed them to be entirely normal. Perimetric fields were normal. Roentgen ray examination of the skull showed convolutional impressions suggesting increased intracranial tension.

Operation revealed an anomalous growth extending from the right tonsil of the cerebellum down the spinal cord below the level of the axis. There was not any operative evidence of increased intracranial tension.

Histologically, the growth was considered to be a heterotopic malformation of the cerebellum with hypertrophy of the right cerebellar tonsil.

Six months later her family reported that she had been partially relieved of symptoms though the fainting attacks have recurred occasionally.

CASE V.—Surg. No. 23999. Glioma of the Ventral Portion of the Medulla. (Protoplasmic Astrocytoma.) A. M. C., a woman aged forty-

two years, entered the hospital because of marked vertigo, nausea, vomiting, diplopia, unsteadiness of gait, and weakness of the right side of the face. The first of these symptoms, vertigo and nausea, beginning three years ago, had become progressively worse and unsteadiness had confined her to bed for over a year. Roentgen rays of the skull failed to show any variation from normal.

Examination of the fundi previous to admission as well as after showed them to be normal.

Exploration of the cerebellar region which was not under any tension revealed a tumor of the right anterior portion of the medulla. Pathologic section showed this to be protoplasmic astrocytoma.

Two years later the patient is able to be about, do a little work, "plays the piano well," and still has no evidence of intracranial pressure.

CASE VI.—Surg. No. 22167. Midline Cerebellar Glioma (Medulloblastoma). W. W. S., a boy aged six years, was admitted complaining of vomiting and difficulty in walking. The history was typical of a midline cerebellar tumor in a child.

For two years he had vomited two or three times a week without apparent cause. This increased markedly some two months prior to admission. Six weeks before he became listless, had difficulty in walking, and complained of severe headache and dizziness. Weakness of all the extremities, especially the right arm, was noted.

Examination showed marked hypotonia, weakness, and emaciation; also nystagmus, a peripheral right facial weakness, right corneal areflexia, and inability to maintain even a sitting posture.

Ophthalmoscopic examination showed slightly hazy nasal margins but no elevation of the disks, though the veins were somewhat full.

Roentgen rays of the skull did not suggest increased intracranial tension.

A cerebellar exploration revealed an internal hydrocephalus and marked foraminal herniation. A midline cerebellar incision came down on a soft reddish tumor, the central mass of which was removed.

The immediate postoperative course was most gratifying. He was discharged nearly symptom free, able to walk well, and gaining rapidly in weight.

Pathologically the tumor proved to be a medulloblastoma—a midline tumor common in children as recently described from this clinic by Dr. Cushing.[37]

For four months he continued to improve but then gradually had a return of all his former symptoms. On readmission six months after the first entry he had very marked cerebellar symptoms with bilateral choked disks.

Reëxploration showed the recurrent growth to be a very vascular one. Death followed an apparently total removal of the growth.

Verified Tumors Without Choked Disk. *B. Of the Cerebrum.* Of the 11 tumors without choked disk located above the tentorium none gave evidence of having been associated with a hydrocephalus. None were of exceedingly great size though some were large enough to collapse the homolateral temporal horn of the ventricle (Case VII). In only one instance (Case XI) could the question of hyperplasia of the tissues of the hemisphere in association with tumor be raised. Six of this number were either temporal or supramarginal and reached the surface or were superficially located. Of the other 5 tumors, 1 was a small parietal meningioma (Case XIII), 3 were parietal lobe gliomas (Cases XIV, XV, XVI), and 1 a parasagittal glioma (Case XVII).

CASE VII.—Surg. No. 22656. Temporal Lobe Glioma (Bipolar Spongioblastoma): Unoperated. N. L., a woman aged forty years, was admitted in a state of coma. Death occurred some twenty-four hours later.

Periodic temporal and right occipital headache which had first led her to consult a physician six months before entry had apparently increased steadily. Diplopia, periods of drowsiness, unsteadiness of gait were complained of for the last ten days of her illness. Three days before admission she lapsed into a state of coma. On admission, respiration was Cheyne-Stokes in character, the right pupil larger than the left, and the left side hemiplegic; a bilateral positive Babinksi and a positive Brudzinski were present. Roentgen rays of the skull were not taken.

Examination of the eyegrounds showed no variation from normal.

Spinal fluid showed 150 cells in which polymorphonuclear leukocytes predominated. The fluid was under normal tension. No organisms were demonstrated by smear or culture.

Necropsy showed a right temporal lobe glioma 6 by 4 cm. on cut section appearing on the surface and attached loosely to the dura in that region. It proved to be a spongioblastoma, bipolar in type (Fig. 1).

FIG. 1.—Case VII. Temporal lobe glioma—Spongioblastoma multiforme in type—unoperated.

CASE VIII.—Surg. No. 21033. Temporal Lobe Glioma (Spongioblastoma Multiforme). J. W. C., a male aged forty-six years, was admitted complaining of constantly increasing attacks of headache, nausea, and vomiting of some eight months' duration.

Physical examination showed a left lower facial weakness, a left positive Babinski. Fundus examination showed no elevation of the disks on entry but an increasing fullness of the veins was apparent from day to day while under observation. Visual fields were normal.

At operation a cystic glioma of the right temporal lobe was exposed and removed in part. The brain was found to be very tense.

The patient left the hospital without any evidence of intracranial tension. He returned two weeks later in a comatose state and with a very tense decompression. The disks were elevated 2 to 3 diopters. A left-sided palsy had supervened. After an extensive further removal of the tumor he made an astonishingly good recovery and three months later was without any evidence of intracranial tension. The tumor which histologically proved to be a spongioblastoma multiforme recurred rapidly and death occurred five months after the first admission.

CASE IX.—Surg. No. 24243. Temporal Lobe Glioma (Spongioglastoma Multiforme). M. G. B., a male aged thirty-nine years, was admitted for the investigation of a complaint of headache, slight mental confusion, and an occasional attack of vomiting. The whole history dated back exactly one month. At the time of admission he showed a slight right lower facial weakness, central in type, slight paraphasia and perseveration.

Fundus examination showed no elevation of the disks, though cupping was difficult to make out.

Visual fields were normal. A left cerebral exploration with decompression disclosed a large subcortical tumor in the temporal lobe which was almost entirely removed. The convolutions showed marked flattening. Pathologically the tumor proved to be a spongioblastoma multiforme.

The tumor was one prone to recur, and on readmission six months later further enucleation of the tumor was made. The disks still showed no evidence of intracranial tension. The subtemporal decompression was soft and depressed. Death occurred some two months later.

CASE X.—Surg. Nos. 23737 and 24186. Temporal Lobe Tumor—Metastatic Carcinoma of Lung. C. D. G., a man aged forty-six years, was operated upon in another clinic with negative findings for the complaint of twitchings of the right side of the face and difficulty in speech of some three weeks' duration. The aphasia progressed after operation and in a short time a right hemiplegia supervened, both of which were present on the first admission here six weeks later. Roentgen rays of the skull did not suggest increased intracranial tension.

Fundi were considered normal. After a Roentgen ray treatment he was discharged. Admitted some two months later in semicoma, the disks showed a choking of 2 to 3 degrees in addition to the other findings. At operation a large partly degenerated temporal lobe tumor was enucleated which on histologic examination proved to be a carcinoma. Subsequent Roentgen rays of the chest showed a mass in the left upper lung area, presumably the primary seat of the growth. Death occurred some four months later.

CASE XI.—Surg. Nos. 4636, 3683, 24047. Supramarginal Glioma with Traces of Calcification and Small Cysts (Oligodendroglioma). M. P. M., a woman aged fifty years, was first admitted to the hospital in 1916 for twitchings of the right side of the face, convulsive seizures, and difficulty in speech, beginning in 1913. Headache was a minor complaint.

On physical examination at that admission, there was a right-sided hypesthesia. A suggestion of fullness of the retinal vessels without measurable disk elevation was noted at that time. Roentgen ray examination of the skull proved negative.

A left cerebral exploration on May 4, 1916, revealed the convolutions which were flattened, thinned and overlapping, especially the two postcentral convolutions. An incision through the cortex to a depth of 2 cm. and needle punctures failed to demonstrate a tumor.

In the nine-year interval before readmission she continued to have convulsive seizures with loss of consciousness until two years ago, when the attacks became less severe. The right arm gradually became spastic, speech more broken, anomia marked, and the patient developed complete word blindness and astereognosis on the right side. Disks have never shown any evidence of choking. Traces of calcification in the tumor were on last admission demonstrated by Roentgen ray.

Reëxploration, in 1925, disclosed a supramarginal glioma containing one or two small cysts, extending down into the temporal lobe. Dr. Cushing's note on its appearance was that a "curiously gray mass which might have been taken for a hypertrophy of the convolutions but it was unmistakably gliomatous in appearance nevertheless." At this exploration, direct evidence of increased pressure was lacking. A block removal of the mass was followed by great improvement in speech, and almost complete return of function of the right side.

Histologically, it proved to be a relatively benign type of tumor, an oligodendroglioma.

In the succeeding two years, she has had minor Jacksonian attacks on the right side and increasing spasticity of that arm but no clinical evidence of increased intracranial pressure.

Case XII.—Surg. No. 24678. Posterior Temporal Lobe Glioma with Calcification in the Tumor (Astroblastoma). F. T. G., a man aged fifty-seven years, was admitted in a comatose state with a history of illness of only seven or eight weeks. This began with mental dullness, ready fatigue, pain over the right eye, and gradually increasing weakness of the left side. On physical examination, the left side was hypesthetic and evidently weaker than the right. Deep reflexes were slightly increased on the left side. The pineal gland was displaced toward the left. The disks were entirely normal. Roentgen ray examination showed a thinning of the bone in the posterior frontal region.

At operation, a tense protruding brain was encountered. The extirpation of a disclosed right posterior temporal lobe tumor was exceedingly difficult and accompanied by bleeding almost beyond control. Reëxploration of the wound done three days later because of a hemiplegia and stupor, showed but little edema and no evidence of postoperative bleeding. The patient died five days after the first procedure.

Pathologically, the tumor proved to be a glioma (astroblastoma) though in gross it resembled a gumma (Fig. 2).

Case XIII.—Surg. No. 24037. Small Parietal Lobe Meningioma with Large Bony Exostosis. J. V. K., a male aged twenty-two years, was admitted for the investigation of a bony swelling on the left parietal region of the skull and generalized headache. They bony exostosis had been noticed for some nine or ten months and headache for a slightly longer period.

Physical examination showed an exostosis of the left parietal bone which was smooth in contour, rising above the level of the outer table of the skull some 2.5 cm., and approximately 8 by 5 cm. in size. There was also a bilateral fine nystagmus, more marked on looking toward the right. Fundus examination showed no variation from normal. Roentgen ray findings were those typical of a meningioma. At operation, a small flat meningioma with a large bony exostosis was encountered and removed en bloc. There was no evidence of increased intracranial tension either at operation or by Roentgen ray examination (Fig. 3).

Case XIV.—Surg. No. 23238. Postparietal Cystic Glioma (Spongioblastoma Multiforme). D. J. McC., a man aged forty-one years, began to

complain of frontal and left-sided headache four months before admission and, shortly afterward, transient numbness and weakness of the right leg. Mental change gradually became apparent and for a few days previous to admission he was completely disoriented, irrational, and showed a tendency to be violent. Marked stupor with a hypesthesia and weakness of the right side were the essential physical findings. Deep reflexes were increased over the affected side.

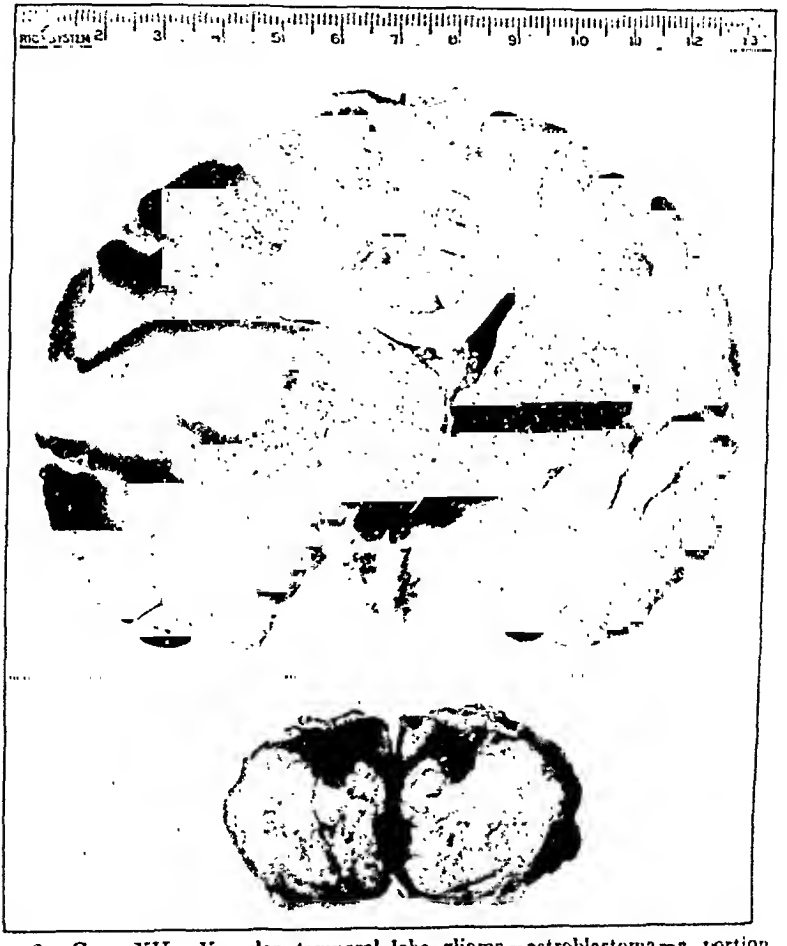

FIG. 2.—Case XII. Vascular temporal lobe glioma—astroblastoma—a portion was removed at operation.

Examination of the fundi showed them to be normal. Roentgen rays of the skull showed a few convolutional impressions suggestive of increased intracranial pressure.

At operation, a large postparietal subcortical gliomatous cyst was encountered. This was fixed with formalin. The convolutions of the brain were much flattened though there was no protrusion of the brain. The patient's death occurred three days later, presumably from cerebral edema. Autopsy showed the cyst to have gliomatous tissue in its walls (Fig. 4).

CASE XV.—Surg. No. 23313. Precentral Cystic Glioma (Spongioblastoma Multiforme). T. C., a male aged sixty-five years, was admitted in a state of coma. The meager history obtained was that of generalized muscular weakness with staggering gait for some six months; ptosis of the right lid was noted four weeks previously. Seven days before entry he was unable to walk because of stiffness and weakness of the left leg. Headache and vertigo had been vague complaints. On examination, there was noted a left-sided spastic paralysis with increased deep reflexes. Examination of the eyeground showed no evidence of choking or tortuosity of the vessels.

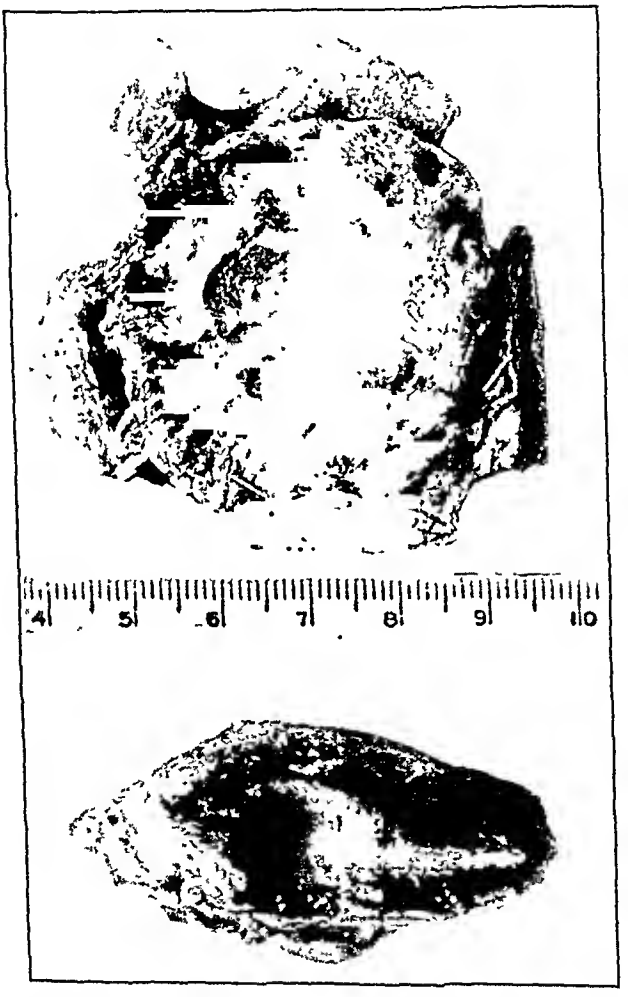

FIG. 3.—Case XIII. Meningioma of parietal region with bony exostosis.

At operation, a cyst was encountered in the right precentral area at a depth of 5 cm., containing 40 cc. of viscid yellow fluid which clotted. The brain at time of operation was not under increased tension. The patient never regained consciousness and died some twenty hours later. Autopsy was obtained (Fig. 5).

CASE XVI.—Surg. No. 22386. Parasagittal Glioma with Small Cyst (Fibrillary Astrocytoma). T. H. J., a man aged thirty-six years, entered complaining of focal Jacksonian seizures involving the left side over a period

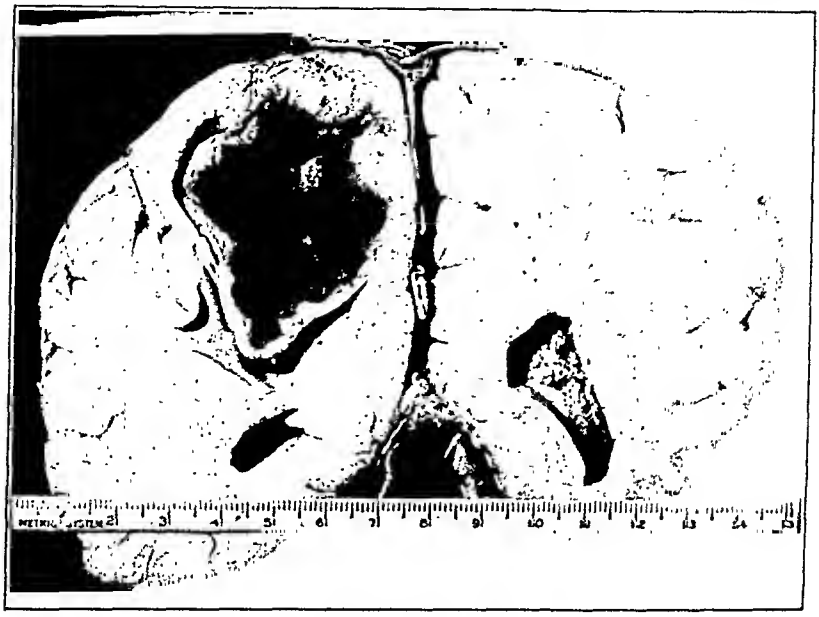

FIG. 4.—Case XIV. Left postparietal cystic glioma—spongioblastoma multiforme. Wall of cyst fixed with formalin at operation three days prior to necropsy.

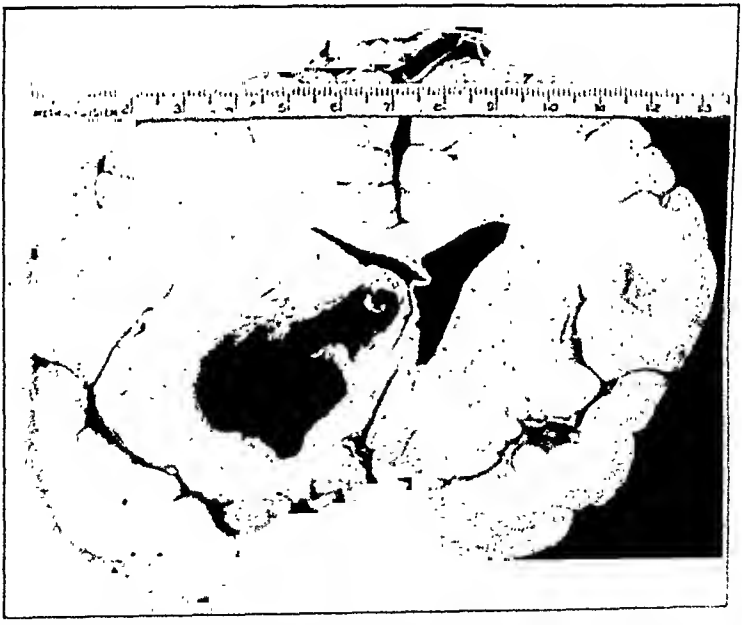

FIG. 5.—Case XV. Right precentral cystic glioma. Spongioblastoma multiforme.

of four years. There had never been pressure symptoms, such as headache and vomiting. On admission, he was found to have weakness and ataxis of the left side, particularly the leg, with increased deep reflexes at the knee and ankle. There was also a hypesthesia over the left leg. On admission the disks were flat but the nasal margins a little hazy. The veins gradually became engorged, the disk margins obliterated and elevation of the disks 1 to 2 degrees. Roentgen rays of the skull demonstrated a generalized thinning of the bones.

A right cerebral exploration was performed with block removal of a cystic glioma from the postcentral parasagittal area. Pathologically, it was a fibrillary astrocytoma, one of the more favorable types of gliomas. The brain at operation was tense.

Three months later he was able to be up and about and using the left hand to some extent. Two years after operation he reports his condition to be stationary though every four to five weeks he is having an attack of unconsciousness. Vision, however, remains good.

FIG. 6.—Case XVII. Parasagittal oligodendroglioma removed at operation.

CASE XVII.—Surg. No. 24395. Parasagittal Glioma (Oligodendroglioma) C. E. H., a man aged thirty-eight years, had been having Jacksonian epilepsy involving the right side for five years.

On physical examination, there was noted a spastic right side, particularly the arm, with increased deep reflexes throughout. There was a slight hypesthesia of the right arm and a complete astereognosis. Speech was a little slow and thick. Disks showed a slight filling up of the cupping but were flat. The veins were normal. Roentgen rays of the skull did not reveal any evidence of increased intracranial tension.

A left cerebral exploration was performed with a grossly total extirpation of a parasagittal oligodendroglioma, a relatively benign type of brain tumor. The brain did not seem to be under increased tension at operation. Convalescence was slow owing to a temporary hemiplegia. Two years later, he reported being able to get about with the aid of a cane and to carry on the work of a general sales manager for his company. He has had a few minor Jacksonian attacks in the interim (Fig. 6).

Unverified Tumors Without Choked Disk. *A. Showing Calcification in the Tumor.* That 6 (23 per cent) of the series of 26 cases without choked disk here reported should show calcification in the brain substance is in itself very striking and warrants a momentary digression. Considering the cerebral tumors alone, for calcification rarely occurs or at least rarely can be detected by Roentgen ray in the cerebellum, the percentage of calcified tumors among those failing to show choked disk rises to 30 per cent.

Calcification in cerebral gliomas as well as other intracranial tumors is deservedly receiving constantly greater attention and assuming a very considerable role in diagnosis—a matter dwelt upon in this clinic by Sosman, Putnam and McKenzie.[38,39] This subject has still more recently been taken up by Van Dessel[40] in his paper on the subject covering cases in this clinic over a five-year period, 1921 to 1925. He reports that 13.5 per cent of verified cerebral gliomas show calcification. In this present year's series there have been 48 cerebral gliomas verified at operation or autopsy. Of this number, calcification was detected by Roentgen ray in 6 (12.5 per cent), which compares well with the series of Van Dessel. Of these verified tumors, 2 existed without evidence of choked disk (Cases XI and XIII). The other 4 instances of calcification occurred in unverified but undoubted cases of brain tumor. In their monograph on the Classification of the Tumors of the Glioma Group, Bailey and Cushing[41] have been able to explain how it is that these tumors showing calcification are lesions with a good prognosis.

CASE XVIII.—Surg. No. 22690. Frontal Lobe Tumor with Calcification. A. D. M., a male aged fifty-eight years, was admitted complaining of generalized convusions. These began six years before entry and were becoming more frequent and severe. Mental change, lapses of memory and responsibility slowly took place over the period of his illness, becoming very marked in the few months prior to entry and totally incapacitating him. He had also experienced slight numbness of the right side of the face and in the right hand with several of the convulsions.

Physical examination was essentially negative aside from evidence of loss of memory, mental slowness, dullness and disorientation. Roentgen rays of the skull showed multiple areas of calcification above the sella and in the left frontal lobe. Fundi were normal. Roentgen rays of the skull were normal.

At operation, a resistant gritty tumor was palpated with a needle 3 to 4 cm. beneath the surface of the left frontal lobe. The brain was not under increased tension.

After a series of Roentgen ray treatments the patient's attacks abated almost entirely, and his mental condition improved so that he was for a short time again able to assume former business responsibilities. Twenty-two months later he was readmitted after being in status epilepticus for forty-eight hours. The disks were still flat although the decompression was under moderate tension. Frontal lobe symptoms are very pronounced. This patient had then been having brain tumor symptoms for six to seven years without ocular symptoms of intracranial tumors.

Case XIX.—Surg. No. 24061. Cerebral Tumor with Calcification. D. L., a girl aged twenty years, entered because of twitching of the left arm and face, generalized convulsions and headache beginning three months previously. She has also experienced numb sensations in the left hand and gradually developed weakness and slight wasting of that hand.

On admission, there was noted a hypesthesia of the left face and arm with inconstant astereognosis; also slight weakness of the left side principally in the arm with increased deep reflexes.

Roentgen rays of the skull showed a calcification, irregular in shape, 3 by 4 cm. in the right hemisphere, 3 cm. medial to the center of the right parietal bone and 2.5 cm. from the midline. There was no evidence of increased intracranial tension. Fundus examination showed hazy nasal borders but no elevation or pathology of the disks.

At a right cerebral exploration, the tumor was palpated with a needle at a depth of 5 cm. but was not explored. The brain was not under increased tension. The decompression remained soft and flat following operation.

Over two years later the decompression is still soft, the disks flat, and eyesight normal. Jacksonian attacks in the left hand and side of the face with an occasional attack of loss of consciousness have continued to date.

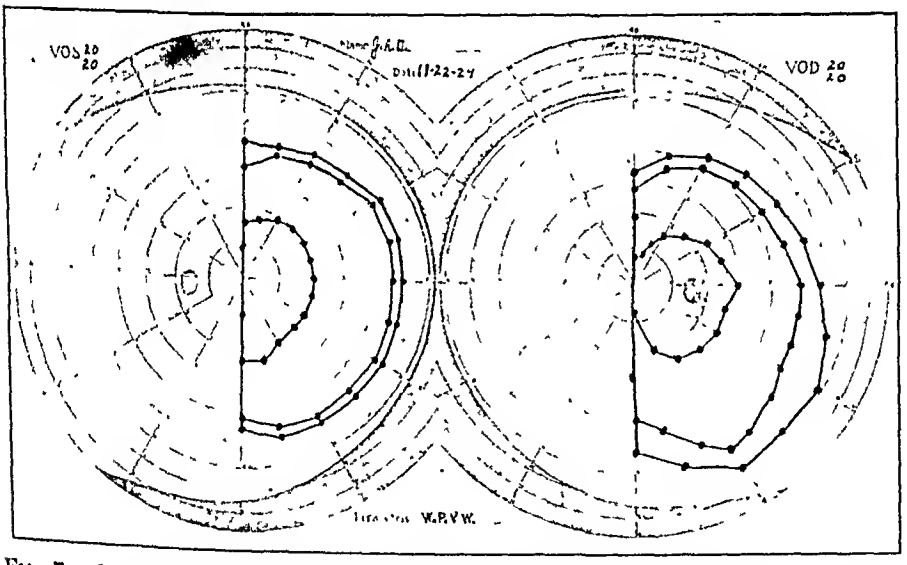

Fig. 7.—Case XX. Left homonymous hemianopsia with preservation of central vision in a temporal lobe calcified tumor—unverified.

Case XX.—Surg. No. 22648. Temporal Lobe Tumor with Calcification and Visual Field Defect. J. A. D., a male aged twenty-eight years, entered because of headache, weakness of the left side and disturbance of vision. This history was a relatively long one. Headache on the right side for four years, diplopia occasionally for three years, and weakness of the left side for six months were the principal symptoms. Sensory changes over the left side had also been noticed.

On physical examination, there was a complete left homonymous hemianopsia (Fig. 7), nystagmus to the right and left, a left-sided spastic weakness with increased deep reflexes, and a positive Babinski on that side.

Roentgen rays of the skull showed an indistinct area of calcification just to the right of the sella in the temporal lobe, approximately 3 by 3 by 5 cm.

The pineal was displaced slightly to the left. There were no convolutional impressions demonstrated by Roentgen ray. Fundi were entirely normal.

Operation revealed the temporal lobe to be bulging, the convolutions flattened, and the Sylvian vessels pushed upward. A resistant mass could be palpated with a needle 4 to 5 cm. beneath the cortex. A puncture through the first temporal lobe convolution 5 cm. deep obtained 5 cm. of slightly xanthochromic fluid.

Observed at intervals for six months, he still shows no evidence of pressure or choking of the disks, though other symptoms persist (Fig. 8).

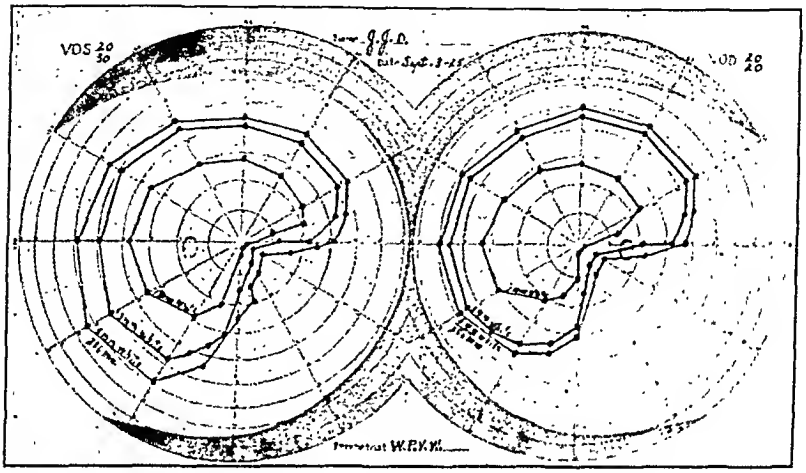

FIG. 8.—Case XXI. Right lower homonymous hemianopsia in a case of a right cerebral tumor with calcification—unverified.

CASE XXI.—Surg. No. 24697. Temporal Lobe Tumor with Calcification and Visual Field Defect. J. J. D., a male aged fifty-seven years, entered for the relief of convulsive seizures, headaches, and difficulty in speech. This trouble had been developing for six years, and very gradually getting worse. Visual hallucinations had been experienced at times.

On admission, he was found to have a right lower quadrantal defect of the visual fields (Fig. 8) and increased deep reflexes on the left side without gross muscular weakness. Anomia was pronounced and astereognosis on the right side was fairly marked.

Roentgen rays of the skull showed a dense irregular calcified spot in the brain substance about 3 cm. deep in the left posterior temporal region, about 3 cm. behind and above the petrous portion of the temporal bone. There was nothing to suggest increased intracranial tension.

Fundus examination showed rather sclerotic disks with hazy nasal borders but no suggestion of choking.

Operation was deferred at the patient's request. Reports of the patient a year and a half later state that he is still having convulsions. Operation has been advised but refused.

These 4 cases, with their prodromal history of from four to six years, well serve to illustrate the relatively benign nature of calcified tumors, as was called attention to by Van Dessel.[4] The extent of the calcification in Case XIX cannot but evidence the

existence of this tumor for many months, even though the history is a relatively short one.

Unverified Tumors Without Choked Disk. *B. Showing Visual Field Defects or Distortion of Ventricles.*

CASE XXII.—Surg. Nos. 23192 and 23580. Left Cerebral Tumor with Visual Field Defect and Distortion of the Ventricles. K. G., a man aged thirty-two years, was admitted for the investigation of frontal headache of some three months' duration.

Routine physical examination revealed a right homonymous hemianopsia, fine rapid nystagmus on looking to the left, and normal fundi. Roentgen rays of the skull were normal. A left cerebral exploration showed a very vascular dura, but no evidence of increased intracranial tension or tumor. The patient was discharged unrelieved to return again in three weeks. At this admission, he was in semicoma. The bone flap was elevated, the decompression tense and disks showed 2 to 3 diopters elevation.

Ventriculograms showed an unexplained slightly dilated ventricle on the right side, a normal appearing one on the left.

Death occurred ten days after admission. Necropsy was not obtained.

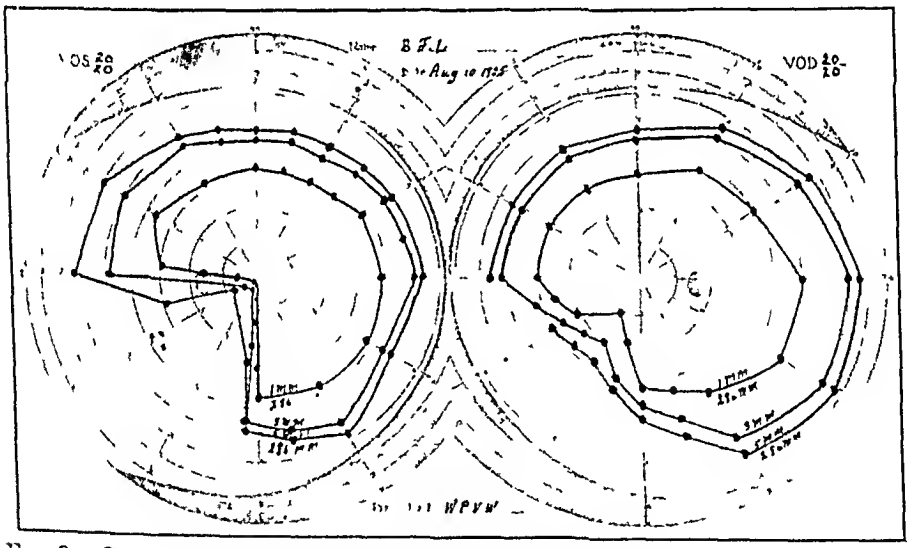

FIG. 9.—Case XXIII. Left lower homonymous hemianopsia associated with temporal lobe-tumor—unverified.

CASE XXIII. Surg. No. 24540. Right Temporal Lobe Tumor with Visual Field Defect. B. F. L., a man aged thirty-six years, entered because of blurring of vision and a left lower quadrant homonymous defect in the visual fields (Fig. 9). In addition he showed a left lower facial weakness, a few nystagmoid jerks to the left, diminished abdominal reflexes on the right side, and a questionable hypesthesia of the left side of the face and body. The fundus examination showed the disks to be normal. Roentgen rays of the skull were negative.

A right cerebral exploration did not reveal any evidence of tumor on the surface.

Physical findings on discharge remained the same as on admission. Six months later visual field examination revealed a still greater homonymous defect than on admission here though he was subjectively free of symptoms.

CASE XXIV.—Surg. No. 23573. Temporal Lobe Tumor with Distortion of Ventricles. G. E., a male aged thirty-eight years, entered because of attacks of petit and grand mal. The attacks of petit mal began two years before admission and the attacks of grand mal some nine months prior to entry. With these he often experienced a sudden peculiar unpleasant taste in the mouth and would smack his lips or try to expectorate. Bitemporal headaches were a minor complaint.

On physical examination, there was a slight hypesthesia of the right side of the face and cornea. Routine Roentgen rays of the skull were negative. Ventriculograms showed the ventricles displaced to the right with elevation and deformation of the left anterior horn. Examination of the fundi showed them to be normal. At operation, the Sylvian vessels and flattened temporal lobe convolutions were found to be pushed upward. The tumor could be palpated with a needle but was not exposed and verified.

He was discharged unimproved. Two years later the patient's condition was reported as essentially the same as on discharge from the hospital.

C. Unverified Tumors—Miscellaneous. CASE XXV.—Surg. Nos. 22676 and 25603. Right Cerebral Tumor—Typical Syndrome. E. J. T., a woman aged thirty-nine years, was admitted. The essential features of this woman's illness were recurrent attacks of numbness involving principally the left face. The arm and leg were affected to a lesser degree. Twitching of the left foot had been noted by the husband for some seven to eight years. There had been an occasional slight nausea and vomiting. Three generalized convulsive seizures, eight days before entry with loss of consciousness and resultant left-sided weakness and hypesthesia brought the patient to the hospital. Visual acuity remained unchanged.

Physical examination revealed a left-sided weakness and hypesthesia with an increased left patellar jerk and a positive Babinski. Abdominal reflexes on the left were diminished. Visual acuity and eyegrounds were entirely normal. Roentgen rays of the skull showed a few convolutional impressions.

A right osteoplastic exploration of the skull revealed a very tense thin dura, flattened convolutions of the brain and a collapsed right ventricle. A bloody tap in the parietal area suggested underlying tumor. The bone flap was sacrificed due to bulging of the brain.

The patient was discharged symptomatically much improved but with physical findings much the same as on admission.

Reëntry ten months later after a series of Roentgen ray treatments showed a persistence of the left-sided spastic hemiparesis. The decompression was depressed. Eyegrounds were normal as before.

Two years after the first admission she was again admitted because of headache, vomiting and failing vision. Examination of the disks showed 2-degree elevation and considerable secondary atrophy. In all, this patient had unmistakable signs of brain tumor for three years before the onset of papilledema. Symptoms which can now be read into the history date back some seven to eight years prior to entry.

CASE XXVI.—Surg. No. 22317. Pineal Gland Tumor—Typical Tumor Syndrome. F. M. Z., a boy aged eighteen years, entered complaining of diplopia, mild headaches, and general malaise. The family and past histories were unessential. Five months prior to admission, he began to suffer persistent diplopia with photophobia and lacrimation. Mild vertical headaches and a feeling of general malaise, though troublesome, did not incapacitate him.

He appeared to be a highly introspective, rather worried and somewhat agitated young adult. Anisocoria and bilateral partial ptosis of the lids

were constant findings. Upward deviation of the eyes on repeated examination was found to be distinctly limited. The pineal gland shadow was in the midline. Roentgen rays of the skull were negative.

Ophthalmoscopic examination showed normal fundi.

A provisional diagnosis of a tumor of the pineal gland was made and he was given seven Roentgen ray treatments.

After discharge, he remained about the same and nine months later still showed a definite limitation of upward movements of the eyes. Reëxamination of the fundi showed them to be entirely normal. Death by suicide occurred about a year after his first admission.

Summary. During the year 1924–1925, there were admitted to the neurosurgical service of this clinic 461 cases, in 365 (79.1 per cent) of which the diagnosis of brain tumor was considered certain or probable. Of this number 145 (40 per cent) were histologically verified at operation or autopsy. In addition to these, 9 per cent have been verified at some previous admission; 22.2 per cent were unverified and 29 per cent were regarded as tumor suspects.

Of this total 145 verified tumors, 11.7 per cent failed to show choked disk at this time of admission to the hospital. If we exclude from this number the pituitary adenomas, congenital cysts, and suprasellar meningiomas—36 in all—which as is well known are rarely associated with choked disk, the percentage rises to 16.5.

Among the 81 unverified cases presenting a full-blown brain tumor syndrome, 9 (11.1 per cent) had normal eyeground when first observed. Failure of the disks to undergo choking does not mean that increased intracranial tension may not have been or be present, for in 50 per cent of the cases reported there was evidence of this either at operation or by Roentgen ray examination. Calcification was demonstrated by roentgenograms in 30 per cent of the cerebral tumors both verified and unverified without choked disk.

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LIVER FUNCTION AS DETERMINED BY BROMSULPHALEIN IN SEVENTY-SIX CASES.

By A. M. Serby, M.D.,
AND
Leon Bloch, M.D.,
CHICAGO.

(From the Otto Baer Fund for Clinical Research of the Michael Reese Hospital and the Nelson Morris Institute for Medical Research.)

Many attempts to estimate the amount of derangement of hepatic function incidental to various diseases have been made by various investigators. The greatest accuracy has been attained by means of studies of alteration of bilirubin and dye excretion.

The bilirubin excretion tests include the van den Bergh,[1] the Fouchet[2] and the icterus index.[3] The van den Bergh affords a quantitative means of estimating serum bilirubin. The qualitative van den Bergh, direct and indirect, differentiates obstructive from the toxic and hemolytic jaundices. The icterus index is a measure of serum pigment, the value of which is lessened by lipoids and the pigments derived from oranges, carrots and other vegetables which cause a change in the color of the serum. Its simplicity and speed recommend it for daily estimation of bilirubinemia. The Fouchet test by the oxidation of bilirubin to biliverdin detects latent jaundice very accurately. It does not differentiate the types of jaundice.

The dye tests are tests of excretion, but since the excretion of such dyes is not a normal physiologic mechanism of the liver, their use is open to theoretical objection. These tests consist in the intravenous injection of a dye and the subsequent detection of the dye in the blood and duodenal contents. It is generally accepted that normally, the liver cord cells remove the dyes from the blood and secrete them into the bile canaliculi. In derangement of the cord cells, the dye remains in the blood to a greater degree than normal and enables one to measure hepatic function.

While investigating the effect of the intravenous injection of dyes, Abel and Rowntree,[4] in 1909, noted that phenoltetrachlorphthalein appeared normally in the duodenal bile in ten minutes. In 1923, S. M. Rosenthal,[5] using phenoltetrachlorphthalein, perfected the first method based on quantitative detection of a dye in serum. This method affords the basis for all dye function tests.

The development of local and general reactions offered two serious objections to the use of phenoltetrachlorphthalein. Many patients developed thrombosis at the point of injection due to vessel-wall damage or indurations from leakage of dye around the vein. Chills and even syncope occurred in other patients. Rosenau,[6] in

1925, summarized these effects. Rosenthal had already realized these drawbacks and in 1925 Rosenthal and White[7] introduced bromsulphalein, a dye which was said to have none of the disadvantages of its predecessor.

Rose bengal or tetraiodotetrabromfluoreseein, another of the allied phthalein products, had been advocated for liver function by Delprat[8] in 1923. Essentially, the technique and results parallel closely those of bromsulphalein. Rose bengal, however, because of an eosin radical in the fluoreseein, may cause hemolysis. The test must be carried out in a dark room. We were unwilling to assume this risk of hemolysis for a test which possesses no advantages over bromsulphalein, and limited our investigation to the latter substance.

Experimental Work. A preliminary study of the local effects of bromsulphalein was made with rabbits. The technique of Rosenau[6] on rabbits' ears was followed, our results being given in Table II for comparison with those of Rosenau with phenoltetrachlorphthalein, which we give in Table I.

TABLE I.—PHENOLTETRACHLORPHTHALEIN.

Solvent.	No dye.	2.5 per cent.	1.2 per cent.	0.6 per cent.	0.3 per cent.	0.15 per cent.
Distilled water	0	Ulcer	Slight ulcer	Marked infiltration	Infiltration	Slight infiltration
Sodium bicarbonate (5 per cent)	0	Ulcer	Slight ulcer	Marked infiltration	Infiltration	Slight infiltration
Sodium carbonate (5 per cent)	0	Ulcer	Slight ulcer	Marked infiltration	Infiltration	Slight infiltration
Normal saline	0	Ulcer	Slight ulcer	Marked infiltration	Infiltration	Slight infiltration

TABLE II.—BROMSULPHALEIN.

Solvent.	5 per cent.	2.5 per cent.	1.2 per cent.	0.6 per cent.	0.3 per cent.	0.15 per cent.
Distilled water	Ulcer	Induration	Induration	0	0	0
Sodium bicarbonate (5 per cent)	Ulcer	Ulcer	Ulcer	Infiltration	0	0
Sodium carbonate (5 per cent)	Ulcer	Ulcer	Ulcer	Infiltration	0	0
Normal saline	Did not dissolve					

The solvents in no case produced an infiltration of the rabbit's ear. Any inflammation aroused was due to the dissolved substance. Distilled water caused the least disturbance with bromsulphalein. Induration occurred with a 2.5 per cent solution in distilled water. With phenoltetrachlorphthalein in this strength an ulcer was formed. Five per cent sodium bicarbonate and sodium carbonate solutions with 2.5 per cent solution of the bromsulphalein produced little inflammation but did not compare favorably with distilled water as a solvent. Normal saline did not dissolve bromsulphalein.

From our experimental results, we regard distilled water a safe solvent for bromsulphalein and its solution in distilled water when injected locally as practically innocuous.

Résumé of Cases. Our work embraced a study of 76 selected cases from the wards of the Michael Reese Hospital. Thirty-two of these were checked by laparotomy or necropsy. In each case a bromsulphalein* determination was made, and where appropriate and possible a qualitative van den Bergh. The presence and depth of icterus, the size, form and consistency of the liver were noted clinically. Each case was watched for forty-eight hours to detect local thrombosis or induration, chills or syncope. The summary is presented in Tables III to XIV. The technique followed in the use of bromsulphalein is the one outlined by Rosenthal and White.[7]

Normally, five minutes following the intravenous injection of bromsulphalein 15 to 35 per cent remains in the blood stream. At thirty minutes, none of the dye can be detected in the blood serum. Increase of the per cent of dye at five minutes or the presence of any dye in the blood stream at thirty minutes constitutes excess retention of the dye and denotes hepatic damage.

Table III presents 11 cases of carcinoma of the head of the pancreas, 7 of which were proven by autopsy or laparotomy. All except one were jaundiced and in all except one the liver was palpable and usually nodular. Most of the cases were late ones with marked jaundice. The case M. D. was very valuable to show the early detection of liver damage by bromsulphalein. All cases showed retention of the dye, from 60 to 100 per cent in five minutes and from 0 to 75 per cent in thirty minutes. The van den Bergh, done in 8 of the cases, showed a delayed direct reaction in 3 and immediate direct in 5. In the 3 cases giving delayed direct positive reaction, obstruction was proven by operation or necropsy and here the van den Bergh should have been an immediate direct, thereby showing the test less reliable than the bromsulphalein.

Table IV includes 9 cases of intraäbdominal malignancy, of which 5 were gastric carcinoma. Six were confirmed by laparotomy or necropsy. In these 9 cases, the value of the test, if any, depended on its revealing liver metastases. The liver showed enlargement or nodules in 6 or 67 per cent of the cases and jaundice was evident in only 1. The van den Bergh, done in 2 cases, failed to give signs of duct obstruction while the bromsulphalein revealed pronounced retention in 5 cases. In 2 of these, M. H. and J. C., the bromsulphalein test proved very valuable in detecting damage of liver function. In 1 case, however, A. S., it failed to be retained despite the presence of a nodular left lobe, which extended to the umbilicus. We conclude that in new growths the bromsulphalein test is very valuable in that it may reveal early hepatic metastases. Its use, however, should be only supplementary to clinical observations.

* The bromsulphalein used in this study was furnished by Hynson, Westcott and Dunning.

TABLE III.—CARCINOMA OF THE HEAD OF THE PANCREAS.

Case and date.	Clinical diagnosis.	Laparotomy or necropsy diagnosis.	Icterus.	Liver.	Van den Bergh.		Bromsulphalein.	
					Direct.	Indirect.	5 min.	30 min.
C. D. A70313 11/28/25	Carcinoma of pancreas	Carcinoma of pancreas; interlobular cirrhosis	++++	Smooth; four fingers below costal margin	+	+	100+	35
L. Z. A60962 12/5/25	Carcinoma of pancreas	Carcinoma of pancreas	++++	Hard; palpable	Delayed trace	+	55	30
E. K. A73701 3/25/26	Carcinoma of pancreas	....	++++	Tender; palpable	Delayed	+	100+	53
4/16/26	Carcinoma of pancreas	....	..	Tender; palpable	...	...	100+	47
I. S. A71690 5/1/26	Carcinoma of pancreas	Carcinoma of pancreas; periportal cirrhosis; echinococcus cyst of liver	++++	Nodular; four fingers below costal margin	Delayed	+	87	63
M. D. A70173 6/17/26	Carcinoma of pancreas	Carcinoma of pancreas	0	Smooth; one finger below costal margin	...	...	85	0
L. A. A79056 10/15/26	Carcinoma of pancreas	Carcinoma of pancreas; liver metastases	++++	Nodular; three fingers below costal margin	+	+	80	57
W. W. A80660 11/3/26	Carcinoma of pancreas	....	++++	Six fingers below costal margin	+	+	100+	75
A. P. A82759 1/20/27	Carcinoma of pancreas	....	++++	Three fingers below costal margin	+	+	100+	73
M. G. A73556 2/10/27	Carcinoma of pancreas	....	++++	Palpable; nodular	...	...	100	75
M. S. A72970 2/27/26	Carcinoma of pancreas	Carcinoma of pancreas	++++	One finger below costal margin	+	+	60	37
N. S. A83638 3/5/27	Carcinoma of pancreas	Carcinoma of pancreas, gall bladder and cystic duct	++++	Not palpable	...	...	80	40
						Average	86	49

TABLE IV.—INTRAÄBDOMINAL MALIGNANCY.

Case and date.	Clinical diagnosis.	Laparotomy or necropsy diagnosis.	Icterus.	Liver.	Van den Bergh.		Bromsulphalein.	
					Direct.	Indirect.	5 min.	30 min.
J. C. A71113 1/16/26	Carcinoma of stomach and liver	Nodular carcinoma involving stomach and liver	0	Right upper quadrant rigid	...	...	100	0
A. S. A72012 1/21/26	Carcinoma of stomach and liver	....	0	Left lobe nodular, tender and extends to umbilicus	...	...	23	0
L. W. A73918 4/15/26	Carcinoma of splenic flexure	Carcinoma of splenic flexure	0	Not palpable	...	...	35	0
H. W. A73095 4/15/26	Hodgkin's disease of stomach	Hodgkin's disease of stomach	0	Not palpable	...	...	35	0
H. B. A73891 4/26/26	Carcinoma of stomach	Carcinoma of stomach	0	Not palpable	...	...	37	0
R. S. A75500 6/11/26	Carcinoma of cervix with metases to rectum and liver	....	0	Nodular; three fingers below costal margin	0	Faint trace	85	27
I. F. A79183 9/29/26	Carcinoma of stomach	....	0	Tender; two fingers below costal margin	...	...	35	0
S. M. A83031 1/29/27	Carcinoma of liver	Carcinoma of liver	0	Nodular; extends to iliac crest	...	...	55	15
M. H. A90958 9/29/27	Carcinoma of stomach	Carcinoma of stomach	Trace	Two fingers below costal margin	0	+	75	0

TABLE V.—HEPATITIS AND CHOLANGITIS. ACUTE AND SUBACUTE.

Case and date.	Clinical diagnosis.	Laparotomy or necropsy diagnosis.	Icterus.	Liver.	Van den Bergh.		Bromsulphalein.	
					Direct.	Indirect.	5 min.	30 min.
C. T. A73017 3/29/26	Acute hepatitis	....	++++	Right upper quadrant tender	+	+	73	35
J. Z. A74555 4/28/26	Acute hepatitis	....	++++	Two fingers below costal margin	Delayed positive	+	100	45
K. S. A74850 5/6/26	Postoperative cholangitis; chronic hepatitis	....	++	Not palpable	...	...	33	27
A. S. A79731 10/20/26	Subacute hepatitis; postoperative cholecystostomy	....	+	One finger below costal margin	...	...	63	10
C. B. AS0723 11/3/26	Sepsis	Cloudy swelling of the liver, kidney and heart and hyperplasia of the spleen	++++	Right upper quadrant rigid	+	+	100+	80
J. D. AS0797 11/5/26	Subacute hepatitis	Pericholecystic adhesions; subacute hepatitis	0	Right upper quadrant rigid	+	+	100	0
11/17/26	Subacute hepatitis	Pericholecystic adhesions; subacute hepatitis	0	Right upper quadrant rigid	...	...	85	0
H. P. AS0819 11/8/26	Acute hepatitis; cholangitis	....	++++	Soft; two fingers below costal margin	0	Slightly positive	55	30
B. D. AS0216 11/20/26	Postoperative cholangitis	Atrophic gall bladder	++	Draining sinus in right upper quadrant	...	...	60	30

E. P. A81497 12/6/26	*Subacute hepatitis, parenchymatous*	Chronic diffuse hepatitis; periportal cirrhosis	++++	Right upper quadrant rigid	+	+	100	80
O. B. A82873 2/2/27	Acute hepatitis; duodenal ulcer	....	+	Not palpable	Delayed positive	+	15	0
W. W. A88964 7/27/27	Acute hepatitis; duodenal ulcer	....	+++	Two fingers below costal margin	+	+	100	55
8/2/27	Acute hepatitis; duodenal ulcer	....	++	Two fingers below costal margin	+	+	65	0
8/8/27	Acute hepatitis; duodenal ulcer	....	+	Two fingers below costal margin	Delayed positive	+	75	0
L. S. A90467 9/8/27	Acute hepatitis; cholangitis	....	++++	Not palpable	+	+	100	85

TABLE VI.—ACUTE CHOLECYSTITIS.

Case and date.	Clinical diagnosis.	Laparotomy or necropsy diagnosis.	Icterus.	Liver.	Van den Bergh.		Bromsulphalein.	
					Direct.	Indirect.	5 min.	30 min.
S. H. A70631 12/10/25	Acute purulent cholecystitis	Acute purulent cholecystitis	+	Not palpable	...	...	80	0
M. L. A72704 2/18/26	Acute cholecystitis	Acute cholecystitis; cystic duct stone	++++	Not palpable	...	...	100	17
J. L. B. A81086 11/17/26	Empyema of gall bladder	Empyema of gall bladder	++++	Five fingers below costal margin	+	+	100	75

TABLE VII.—CHRONIC CHOLECYSTITIS.

Case and date.	Clinical diagnosis.	Laparotomy or necropsy diagnosis.	Icterus.	Liver.	Van den Bergh.		Bromsulphalein.	
					Direct.	Indirect.	5 min.	30 min.
M. H. A71569 1/6/26	Chronic pancreatitis; chronic cholecystitis	Chronic cholecystitis; chronic pancreatitis	0	Edge palpable	...	...	37	0
H. K. A71679 1/11/26	Chronic cholecystitis	....	Trace	Right upper quadrant tender	...	...	25	0
M. M. A86061 5/20/27	Chronic cholecystitis; postoperative cholecystostomy	Chronic pancreatitis; acute pancreatitis	0	Draining cystic duct	0	Delayed positive	15	0

TABLE VIII.—COMMON DUCT OBSTRUCTION.

Case and date	Clinical diagnosis.	Laparotomy or necropsy diagnosis.	Icterus.	Liver.	Van den Bergh.		Bromsulphalein.	
					Direct.	Indirect.	5 min.	30 min.
L. R. A73137 3/21/26	Common duct stone; diabetes mellitus	....	++	Not palpable	Delayed positive	+	75	43
L. E. A73519 3/25/26	Common duct stone	....	++++	Right upper quadrant mass	...	...	85	0
J. F. A75999 6/11/26	Stenosis of common duct; chronic cholecystitis; chronic pancreatitis; peptic ulcer	Stenosis of common duct; chronic cholecystitis; chronic pancreatitis	+++	Not palpable	...	...	45	35

TABLE IX.—CIRRHOSIS OF THE LIVER.

Case and date.	Clinical diagnosis.	Laparotomy or necropsy diagnosis.	Icterus.	Liver.	Van den Bergh.		Bromsulphalein.	
					Direct.	Indirect.	5 min.	30 min.
F. S. A70557 12/3/25	Cirrhosis of liver; chronic cholecystitis	Cirrhosis of liver; chronic cholecystitis	0	Right upper quadrant tender	...	...	25	0
J. M. A73330 3/11/26	Syphilitic hepatitis		++++	One finger below costal margin	...	...	83	57
3/20/26	Syphilitic hepatitis	....	+	One finger below costal	...	...	30	0
J. C. A81110 11/19/26	Laennec's cirrhosis	....	++	Palpable	+	+	100	75
L. R. A88219 7/6/27	Cirrhosis of liver; Paget's disease	....	0	Nodular; three fingers below costal margin	0	0	35	0

TABLE X.—BLOOD DISEASES.

Case and date.	Clinical diagnosis.	Laparotomy or necropsy diagnosis.	Icterus.	Liver.	Van den Bergh.		Bromsulphalein.	
					Direct.	Indirect.	5 min.	30 min.
D. P. A82347 1/8/27	Pernicious anemia	....	Trace	Not palpable	...	...	18	0
L. B. A75307 6/12/26	Polycythemia vera*	....	0	Four fingers below costal margin	...	...	90	0
S. D. A73078 3/3/26	Congenital hemolytic icterus	Fibrous splenomegaly	Trace	One finger below costal margin	0	+	25	0
S. B. A80284 11/3/26	Aleukemic leukemia	Aleukemic leukemia	0	Right upper quadrant mass	...	...	35	0
T. M. A90161 9/10/27	Aleukemic leukemia	Aleukemic leukemia; splenomegaly	0	Two fingers below costal margin	0	+	25	0
E. B. A88120 7/7/27	Chronic lymphatic leukemia	..	0	Ten centimeters below costal margin	0	Delayed positive	60	0
J. E. A80274 10/18/26	Banti's disease (late)	..	Trace	Three fingers below costal margin	Delayed positive	+	77	0
B. S. A82586 1/7/27	Banti's disease (early)		0	Soft, regular; four fingers below costal margin	...	...	10	0

* This case had a local reaction.

TABLE XI.—HEART DISEASE.

Case and date.	Clinical diagnosis.	Laparotomy or necropsy diagnosis.	Icterus.	Liver.	Van den Bergh.		Bromsulphalein.	
					Direct.	Indirect.	5 min.	30 min.
M. K. A69853 12/10/25	Subacute bacterial endocarditis	....	0	Not palpable	...	...	30	0
M. K. A70602 12/11/25	Cardiac asthma; chronic myocarditis	....	0	Not palpable	...	...	30	0
G. U. A66498 12/11/25	Chronic myocarditis; luetic aortitis	Chronic myocarditis; luetic aortitis	Trace	Smooth; four fingers below costal margin	...	...	30	0
W. W. A75894 6/12/26	Fibrous myocarditis	Fibrous myocarditis; chronic interlobular hepatitis	Trace	Smooth; moderately enlarged	...	...	100	0
J. W. A75870 6/14/26	Chronic myocarditis	Chronic myocarditis	0	Not palpable	...	...	15	0
L. G. A70466 12/4/26	Arteriosclerosis	. . .	0	Smooth; three fingers below costal margin	...	...	30	0
L. B. A70821 12/8/26	Chronic myocarditis; auricular fibrillation	. . .	0	Right upper quadrant tender	...	...	30	0
A. S. A70463 12/9/26	Cardiosclerosis; auricular fibrillation; anasarca	....	0	Smooth; four fingers below costal margin	...	. .	30	0
H. H. A85898 5/2/27	Chronic myocarditis; chronic cholecystitis; jaundice of cardiac origin	....	++	Smooth; three fingers below costal margin	+	+	75	25

TABLE XII.—GASTRIC ULCER.

Case and date.	Clinical diagnosis.	Laparotomy or necropsy diagnosis.	Icterus.	Liver.	Van den Bergh.		Bromsulphalein.	
					Direct.	Indirect.	5 min.	30 min.
H. H. A70168 11/29/25	Bleeding gastric ulcer	Chronic gastric ulcer; subacute gastritis; perihepatitis	0	Not palpable	...	...	30	0
S. A. A70295 12/3/25	Bleeding gastric ulcer	....	0	Not palpable	...	...	25	0
A. C. A70140 11/25/25	Bleeding gastric ulcer	..	0	Not palpable	...	...	35	0

TABLE XIII.—LATE TOXEMIA OF PREGNANCY.

Case and date.	Clinical diagnosis	Laparotomy or necropsy diagnosis.	Icterus.	Liver.	Van den Bergh.		Bromsulphalein.	
					Direct.	Indirect.	5 min.	30 min.
P. A. A72947 3/1/26	Late toxemia of pregnancy; hypertension	....	0	Not palpable	...	...	33	0
P. J. A75908 3/8/26	Late toxemia of pregnancy; hypertension	....	0	Not palpable	...	...	25	0

TABLE XIV.—MISCELLANEOUS.

Case and date.	Clinical diagnosis.	Laparotomy or necropsy diagnosis.	Icterus.	Liver.	Van den Bergh.		Bromsulphalein.	
					Direct.	Indirect.	5 min.	30 min.
J. H. A69828 12/15/25	Syphilis; compound fracture of tibia and fibula	....	0	Not palpable	...	...	15	0
D. J. A70635 12/15/25	Recurrent inguinal hernia	....	0	Not palpable	...	...	25	0
A. M. A70027 12/18/25	Endocrine dyscrasia	....	0	Not palpable	...	...	35	0
J. C. A71078 12/18/25	Bruise of lumbar muscles	....	0	Not palpable	...	...	20	0
H. L. A71902 1/13/26	Benign tumor at pylorus	Pancreatic adenoleiomyoma of gastric wall	0	Right upper quadrant tender	...	...	33	0
A. L. A73225 3/27/26	Tumor of larynx	....	0	Not palpable	...	...	25	0
B. W. A81685 12/7/26	Acute alcoholism	....	0	Not palpable	...	...	35	0
B. B. H70719 12/8/26	Acute bronchitis	....	0	Not palpable	...	...	30	0
H. B. A70141 3/19/27	Fibrosis of the neck of the bladder	....	0	Not palpable	...	...	35	0

Table V includes 12 cases of acute or subacute hepatitis and cholangitis of which 4 were confirmed by operation or necropsy. Eleven were clinically icteric. In 9 cases a van den Bergh was done. According to McNee[1] the van den Bergh in this group usually shows a delayed direct reaction and an immediate indirect reaction. In marked damage, the van den Bergh may be an immediate direct. In 6 of these 9 cases the van den Bergh was immediate direct. The bromsulphalein showed in these cases a very high per cent of retention, also denoting extreme damage to the liver cord cells. In 10 of the cases, examination of the right upper quadrant revealed abnormal findings. The bromsulphalein with the exception of 2 cases showed uniformly high retention, above 55 per cent for the five-minute period and usually a measurable amount for the thirty-minute period. In the case of O. B. the diagnosis was aided by the van den Bergh and not by the bromsulphalein. In 2 cases, J. D. and W. W., the tests were repeated within twelve days and although improvement was noted, complete return of liver function had not occurred. To summarize, in this group the bromsulphalein added nothing to the clinical examination. It was valuable as confirmatory evidence.

Table VI comprises 3 cases of acute cholecystitis, all icteric and with marked dye retention. Examination in these cases revealed tenderness and rigidity, and in 1 case a mass in the right hypochondrium. In 2 of these, empyema of the gall bladder was found and in the third, stones were found in the gall bladder and cystic duct but not in the common duct.

Table VII shows 3 cases of chronic cholecystitis, with no icterus in 2 cases and a trace in the third with no excess retention of the dye. This agrees with the clinical findings.

Table VIII contains 3 cases of common duct obstruction, all icteric and showing a definite bromsulphalein retention. This latter information added nothing to the clinical diagnosis.

In Table IX are 4 cases of cirrhosis of the liver, 2 of which were icteric and in all of whom the right upper quadrant showed abnormality. The 2 patients with icterus gave a positive van den Bergh and retained the dye. Therefore, in this group also, the bromsulphalein appeared of confirmatory value only.

Table X includes 8 cases of blood disease. Three were jaundiced. In all except 1, the liver was palpable. The van den Bergh was done in 4, 3 of which gave the negative direct and positive indirect reaction as expected and diagnostic of an hemolytic icterus. One would expect that bromsulphalein would not be retained excessively in any of this group. In 3, however, one of polycythemia vera, another of chronic lymphatic leukemia and a third of far advanced Banti's disease, the liver had been so changed that the bromsulphalein was excessively retained. In the late Banti's disease just mentioned the van den Bergh test showed a delayed immediate positive. This

is in accord with the bromsulphalein test. Attention is also called to the difference between early leukemia and chronic leukemia, and between early and late Banti's disease as to liver function; the more chronic the disease and the greater its duration, the more marked is the dye retention.

In the case of polycythemia vera of this group occurred the only local reaction in the entire study. In this case the vein was easily found and the bromsulphalein quickly injected with no leakage into the perivascular tissues. In twenty-four hours, a slight tenderness, and in forty-eight hours, a definite thrombosis with local tenderness and swelling occurred at the site of injection. No chills accompanied this. In a week this local inflammation had disappeared with no permanent damage to the tissues. Inasmuch as this disease is characterized by ease of trauma to vessel wall, it is quite possible that venipuncture without bromsulphalein injection would have produced the same result.

Table XI contains 9 cases of heart trouble, 3 of which were icteric. In 6, marked enlargement of the liver occurred, but in only 2 of these 6 was there retention of the dye above the normal.

Table XII includes 3 cases of bleeding gastric ulcer, none icteric and none showing liver enlargement. All had normal liver function.

Table XIII includes 2 cases of late toxemia of pregnancy. Neither was icteric or showed liver enlargement. No abnormal retention of the dye was noted.

In Table XIV is gathered a group of 9 cases intended for control or which could not be included with the preceding groups. None was icteric or showed an enlarged liver. The bromsulphalein test was within normal limits.

Discussion. The bromsulphalein test is of value to measure liver function quantitatively. In some conditions it does not have the differential diagnostic value claimed for the van den Bergh reaction. In clinically recognizable cases of cirrhosis where nodular enlargement of the liver is present, the test may be of no value. Likewise, in chronic cholecystitis, it is of no value. Attention is called, however, to one peculiarity of the test in diseases of long duration affecting the liver. In carcinoma of the head of the pancreas, which is associated with jaundice of long duration and is marked by chronic dilatation of the bile ducts with compression of hepatic tissue, a uniformly high ratio of the five-minute average to the thirty-minute average is found. The average for our group of 12 such cases was 86 per cent for five minutes and 49 per cent for thirty minutes, a ratio of 1.77 to 1. The same observation is made in patient K. S. with a diagnosis of chronic hepatitis. The bromsulphalein reading was 33 per cent in five minutes and 27 per cent in thirty minutes. In J. F., a case of chronic hepatitis and pancreatitis, the values were 45 and 35 per cent. In these cases there appears to be a tendency for the dye to be excreted at about the normal rate

during the first five minutes with very little additional excretion during the remainder of the thirty minutes.

In obstructive jaundice, as caused by carcinoma of the head of the pancreas, stenosis of the common bile duct by fibrosis or closure of the duct by a stone, the history and the bilirubin and dye tests agree. The dye test has no distinctive value.

In hepatitis and cholangitis the van den Bergh test is not definite, but the bromsulphalein test shows retention of the dye in some cases. This is important in calling attention to liver damage.

In malignancy in the absence of apparent icterus or a positive bilirubin test, the bromsulphalein has occasionally proven valuable in detecting liver damage due to metastases. This, however, does not always hold true and a negative test does not rule out metastases.

In diseases of the blood, characterized by icterus, large liver and spleen, and a negative direct and positive indirect van den Bergh, the bromsulphalein test is negative in early cases. In long-standing cases, the liver may become sufficiently damaged to show decreased function by the bromsulphalein test. This finding is highly important in the prognosis. The van den Bergh is not as accurate in eliciting evidence of liver damage in this class of patients.

In conjunction with other tests, particularly the van den Bergh, the bromsulphalein test is of considerable confirmatory value. It is our belief that the tests should be complementary to each other and supplementary to the clinical findings. Each test possesses value because the one, the van den Bergh, determines an excess of a normal constituent of the blood, bilirubin, and the other, bromsulphalein, registers the excretory function of a phthalein product by the liver. In 30 cases, the bromsulphalein showed retention in 7 or 22.6 per cent where the van den Bergh was normal. *Vice versa*, the van den Bergh was positive in 2 cases or 6.6 per cent where the bromsulphalein was negative. We, therefore, believe that although the bromsulphalein test proved more valuable, both should be used.

Conclusions. 1. An experimental study of the toxicity of bromsulphalein showed it to have little local toxicity.

2. Seventy-six cases were studied in which the presence of icterus, the size and form of the liver, the results of bromsulphalein and in some cases, the van den Bergh test were noted. Of these, 32 cases were checked by laparotomy or necropsy.

3. Bromsulphalein is valuable in detecting liver metastasis and physiologic depression of liver function following chronic diseases, as chronic hepatitis of nonspecific origin, cirrhosis, Banti's disease, leukemia, and so forth.

4. The bromsulphalein test in 76 cases after being injected intravenously did not produce a general reaction. Local thrombosis occurred in only 1 case, one of polycythemia vera, in which disease thrombosis easily occurs.

5. A complementary use of the bromsulphalein and the van den Bergh test may prove valuable in some instances.

6. No test of liver function can in any way supplant clinical methods of observation.

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UNCERTAINTIES OF CHOLECYSTOGRAPHY.

By W. W. Boardman, M.D.,
San Francisco, Calif.

(From the Medical Clinic, Stanford University Medical School.)

Cholecystography has brought to the diagnosis of gall bladder disease a degree of certainty never before obtained. There is, however, serious question as to whether this certainty is as absolute as some of the recent reports indicate.[1] From these reports it would seem that a failure of the gall bladder to visualize after the administration of tetraiodophenolphthalein is taken as absolute proof of the presence of a pathologic gall bladder, and an equally definite indication for cholecystectomy. The general acceptance of such teachings is certainly not warranted, and would do much harm both to cholecystography and to the suspected gall bladder patient.

It must be emphasized that cholecystography is not a divining rod for the recognition of pathologic gall bladders, but is merely a procedure by which some of the functional activities of the biliary system may be studied. Thus, a successful gall bladder visualization rests upon the following six factors: (1) A sufficient concentration of the dye in the blood stream; (2) a liver capable of excreting the dye; (3) patent common and cystic ducts; (4) a gall bladder capable of receiving and discharging the dye; (5) a gall bladder capable of concentrating the dye; (6) a properly functioning sphincter mechanism at the lower end of the common duct. A disturbance

in any one of these six factors would result in a partial or complete failure of gall bladder visualization; yet several of them are entirely independent of the anatomic condition of the gall bladder.

Briefly reviewing these various factors, it is apparent that a sufficient concentration of the dye in the blood stream is of prime importance. The intravenous method with known dosage obviously answers the requirement; the oral method as obviously introduces the uncertain factor of intestinal absorption, which in the individual case cannot be dismissed. A failure to visualize after the oral administration, therefore, demands a repetition of the test by the oral, or preferably by the intravenous, method before concluding that a disturbance in the biliary system exists.

As the excretion of the dye is dependent upon the functional activity of the liver cells, it is evident that with widespread liver damage partial or complete failure of gall bladder visualization might result from poor excretion of the dye, even in the presence of a functionally normal gall bladder.

Obstruction in the common or cystic duct will obviously interfere with the excretion of the dye by the liver or with its entrance into the gall bladder.

If the lumen of the gall bladder be filled with stones, polypi, new growths and so forth, or if the wall be thickened and inelastic, little or no dye will gain entrance to the gall bladder, and a failure naturally results. Whether or not a normal gall bladder may be filled with concentrated bile at the commencement of the test so that dye in sufficient concentration to give a normal visualization fails to appear within the gall bladder, seems worthy of consideration.

The concentration of the dye in the gall bladder is essential to a normal test. Presumably this is a function of the wall, but the exact mechanism is as yet unknown. Chandler and Newall,[2] in a careful study of surgical material, were entirely unable to correlate the pathologic lesion with the degree of concentration of the dye, some cases with extensive destruction of the mucosa showing practically normal concentration, whereas others with practically normal mucosa showed poor concentration. These findings are of interest in connection with Winkenwerder's[3] recent work which demonstrated that in the cat, at least, there is considerable absorption by the lymphatics of the subepithelial stroma.

The factor of the sphincter mechanism at the lower end of the common duct has not received the attention that it demands in connection with this test. It is established that the lower end of the common duct must be tonically contracted in order that freshly secreted bile may find its way through the cystic duct into the gall bladder. Without this closure of the lower end of the common duct the liver bile flows directly into the duodenum. We accept that the sphincter of Oddi is tonically closed during the interdigestive periods, preventing the passage of bile into the duodenum;

but that during the digestive periods, in response to various stimuli, it relaxes, allowing the discharge of bile. As a matter of fact, we know very little of this sphincter mechanism and of its control, yet the accuracy of the test depends upon the proper functioning of this sphincter. Is it not possible that this sphincter relaxes in response to reflex stimuli from the stomach, duodenum, colon and so forth, and that occasionally, at least, failure of the test results from the faulty functioning of the sphincter, rather than from gall bladder pathology?

The following case reports are of interest in this connection. The usual details of the clinical histories are omitted, as our interest is in the cholecystographic findings:

Case Reports. CASE I.—Mrs. H. J. T. No. 161582, Stanford Hospital.
February 16, 1927: Tetraiodophenolphthalein intravenously produced. *No visualization.*
March 24: Tetraiodophenolphthalein intravenously produced. *Normal visualization.*

CASE II.—Mrs. G. O. No. 159907, Stanford Hospital.
February 1, 1927: Tetraiodophenolphthalein intravenously produced. *Incomplete visualization;* very poor concentration, less than 0.5 per cent.
February 10: Tetraiodophenolphthalein intravenously produced. *Normal visualization;* normal concentration, 2 per cent.

CASE III.—Mrs. M. G. No. 161807, Stanford Hospital.
March 24, 1927: Tetraiodophenolphthalein intravenously produced. *Incomplete visualization;* poor concentration, less than 0.5 per cent.
March 30: Tetraiodophenolphthalein intravenously produced. *Normal visualization;* concentration, 2 per cent.

CASE IV.—Mrs. G. B. No. 137141, Stanford Hospital.
February 20, 1925: Tetraiodophenolphthalein intravenously produced. *No visualization.*
February 26, 1926: (After one year of medical treatment, including Lyon's treatment.) Tetraiodophenolphthalein intravenously produced. *Normal visualization.*

CASE V.—J. S. No. 150178, Stanford Hospital.
April 7, 1927: Tetraiodophenolphthalein intravenously produced. *Normal visualization.*
July 27: Tetraiodophenolphthalein intravenously produced. *No visualization.*

CASE VI.—Miss W. Private record.
May, 1926: Tetraiodophenolphthalein intravenously produced. *No visualization.*
May, 1927: Tetraiodophenolphthalein orally produced. *Normal visualization.*

From these case reports, although few in number, it is evident that a repetition of the Graham test within a few days, or after several months, may fail to confirm the findings of the original test.

This emphasizes the fact already stated that cholecystography is a test of the functional activity of the biliary system at a particular time, rather than a test of the more or less permanent anatomic condition of the gall bladder.

It, therefore, follows that cholecystographic findings must be interpreted in terms of function of the biliary system rather than in terms of pathology of the gall bladder.

Conclusion. From this brief review it is apparent that factors other than the anatomic condition of the gall bladder play a part in determining the results of cholecystography; that some of these factors may vary from day to day, and so give contradictory results on a repetition of the test; that cholecystographic findings must be interpreted in terms of functional activity of the biliary system rather than in terms of pathology in the gall bladder; finally, that, although cholecystography is of the greatest aid in the study of the functional activity of the biliary tract, careful correlation of these findings with the other clinical findings is absolutely essential to proper diagnosis and treatment.

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NONGONORRHEAL NONTUBERCULOUS EPIDIDYMITIS.

By Meredith F. Campbell, M.D.,
New York.

(From the Urological Service of Bellevue Hospital.)

Nongonorrheal nontuberculous epididymitis is of such frequent incidence and is characteristically so prone to suppuration with secondary necrosis of the testicle that early diagnosis becomes a matter of prime importance. This type of epididymitis is more commonly yet incorrectly designated as "nonspecific." Nor is the disease an orchitis except as collateral inflammatory testicular involvement may be present. The morbidity is high, since sterility follows bilateral inflammation in most cases and suppurative extension from the epididymis sacrifices many testes. In a recent study of 3606 cases of epididymitis admitted to the Urologic Service of Bellevue Hospital we found that 3000 were gonorrheal in origin. 280 were due to the tubercle bacillus and the remainder, 326 or approximately 9 per cent, were of other etiology. It is the latter group that we wish to consider here. While three-fourths of these will recover without surgical intervention, 1 in 4 require operation and a third of these will lose the testicle.

Although the etiology is variable, these lesions are predominantly the result of pyogenic bacterial invasion. The organisms most frequently encountered are staphylococci, streptococci and colon bacilli. The Bacillus mucosus capsulatus of Friedländer and the Micrococcus catarrhalis are less often etiologically associated. Sometimes the infection is blood borne. We have seen epididymitis in 1 case each of pneumonia, influenza and acute tonsillitis and in no other manner than by bacterial metastasis could the lesions be accounted for. Others have reported similar observations.

In 1 of every 15 cases a history of trauma was obtained, most frequently a kick or a straddle injury. A more common form of trauma is that of injury to the posterior urethra by catheterization or other instrumentation. Vigorous prostatic massage may accomplish this so that in the presence of even a mild posterior urethral or prostatic infection an epididymitis may be incited. Many of these patients have suffered previously with gonorrhea and have been left with a residual nongonorrheal posterior infection so commonly associated with yet outlasting the gonorrhea. This, and the transportation of infection by the urinary tract, from a diseased kidney, for example, explains the presence of posterior urethral infections in those cases of otherwise obscure etiology. In this series certain patients had suffered instrumental trauma outside the hospital, but we have not included epididymitis developing during indwelling or intermittent catheterization nor when appearing subsequent to prostatectomy. The colon bacillus can be isolated from most lesions of this nature and a third are grossly suppurative.

Nongonorrheal nontuberculous epididymitis is of greatest incidence in early adult life attacking those of the third decade with relatively lesser and those of the fourth decade with relatively greater frequency than gonorrheal epididymitis. The ages of our patients are indicated in Table I. We found involvement of the right side

TABLE I.—AGE OF PATIENTS.

Years.	Surgical.	Total.
19 and under	1	3
20 to 29	25	111
30 to 39	25	137
40 to 49	17	49
50 to 59	8	18
60 to 69	1	3
Not recorded	2	5
	79	326

in 157, in the left in 148 bilateral involvement in 19 patients. The present attack was a recurrence in 99 cases. Many had suffered from gonorrhea previously (Table II and III), but its presence at the time of hospital admission was ruled out in all cases of this series.

TABLE II.—GONORRHEAL INFECTIONS.

No. of attacks.	No. of cases.	Most recent attack	No. of cases.
1	29	Within 2 years	1
2	3	2 to 5	7
3	2	6 to 10	10
4	1	11 to 15	7
Over 5	2	Over 15	10

TABLE III.—PREVIOUS EPIDIDYMITIS.

No. of attacks	No. of cases.	Months.		Years since last attack.			
		2 to 6	7 to 12	1 to 2	3 to 5	6 to 10	over 10
1	70						
2	18	5	21	38	25	5	5
3	6						

The epididymitis onset is usually abrupt, but, as a rule, the initial symptoms are not as acute as in the gonorrheal variety. On the other hand, we have observed some patients who were extremely ill and suffered greatly. Because of the milder onset and because external evidence of urethral infection is lacking, the severity of the disease is unappreciated by the patient and, not infrequently, by the physician as well. Therefore, the average duration of the lesion before search of special treatment is longer than with the gonorrheal type, and when the patient is first examined a gross abscess is not only often present but occasionally has already ruptured. The duration of the disease before our patients entered the hospital is indicated in Table IV. The gradual onset

TABLE IV.—DURATION OF EPIDIDYMITIS PRIOR TO HOSPITAL ADMISSION.

Days.	Cases.	Weeks.	Cases.	Months.	Cases.	Years.	Cases.
1	22	1	39	1	13	1	5
2	14	2	17	2	23	2	
3	48	3	35	3	26	3	3
4	33	4	..	4	3	4	
5	32	5	14	5	4	5	
6	22			6	3	6	2
7–10	25						
11–15	21						

and absence of marked symptoms in some cases clinically resembles tuberculous infection and the epididymitis is often transported several months before gross suppuration or sinus formation arrests the attention of the patient.

All varieties of epididymitis may bear striking similarities; the onset and immediate course of gonorrheal, nonvenereal and tuberculous epididymitis may be clinically indistinguishable. Gonorrheal epididymitis resolves most rapidly, nongonorrheal epididymitis disappears more slowly and is four times as prone to suppuration, while the subsequent course of tuberculous epididymitis may cover a period of many months or years. Occasionally the nongonorrheal nontuberculous type may be of such long duration that diagnostic differentiation from tuberculous disease can be made only by tissue examination.

Symptoms. Pain and swelling are the chief symptoms in all cases. Pain may be extreme, best described as sickening in character and is often most severe along the spermatic cord or is referred to the groin, loin, abdomen, lower back or rectum. Frequently the patient is aware of precursory inguinal discomfort along the cord or an ache or sharp stabbing pain localized in the epididymis a few hours before the acute outset. Cord pain, while due in part to the testicular drag on the inflamed funicular tissues is primarily the result of edematous swelling within the confines of the funicular sheath and the inguinal canal. Pain is increased by motion and the forward stoop and straddle gait afford a characteristic walking attitude. As testicular elevation will relieve, patients often manually support the scrotal contents. On the other hand, in many cases the disease runs an essentially assymptomatic course. The patient may be aware of only the slightest discomfort and unquestionably the lesion in these mild cases is frequently the precursor of a subsequent hydrocele. In a recent study of 500 cases of hydrocele we[1] observed that postinflammatory changes in the epididymis were nearly always present, and most of these patients could recall no antecedent inflammation of the scrotal contents. In some cases, however, the onset of the hydrocele followed an acute epididymitis.

The acute symptoms persist until: (1) Resolution begins, or (2) rupture of the epididymis by suppuration releases the intracapsular tension with relief from pain. With institution of proper treatment three-fourths of these cases will be at once relieved and promptly recover; the remainder will require operation.

Diagnosis. If the epididymitis is acute the scrotum is usually reddened—a rather purplish hue—swollen, tense and shiny. Exquisitely tender to touch, the patient will rarely permit extensive palpation. It will be determined, however, that the disease is of the epididymis and not of the testicle—an important point. If early, the globus minor only is involved, but the inflammation usually becomes universal subsequently. Funiculitis may be marked, the cord is often of thumb size thickness and highly sensitive. The vas deferens shows a variable degree of involvement; sometimes it is 1 cm. in diameter. If the disease is subacute tenderness is less marked and careful palpation will disclose generalized induration or, at times, localized abscess in the epididymis. When the condition has become chronic the scrotum usually appears normal, but may sometimes present discharging fistulous orifices. At this stage irregular nodulation or beading of the vas is a not uncommon finding.

Rectal examination reveals an inconstant degree of prostatitis and vesiculitis. Occasionally these will be palpably normal. Particularly interesting are those cases showing contralateral seminal vesicle involvement. This we observed four times. As a rule, the more chronic the epididymitis, the more indurated does the prostate become. Prostatic changes are more often noted than are indurations of the vesicles (Table V).

TABLE V.—CONDITION AS EVIDENCED BY PHYSICAL EXAMINATION.

	Enlarged.	Indurated.	Tender.	Abscess.	Negative.
Cord	36	25	30	..	3
Prostate	18	26	2	1	6
Sem. vesicles	10	29	..	..	8
Testicle	4				
Vas	11	11 (nodular 4) (abscess 1)			

The differential diagnosis is frequently extremely difficult and often not made without histologic examination of the epididymis. Clinically, in most cases, an inflammatory induration of the epididymis and a palpably normal testicle indicates clearly the lesion is not an orchitis. Hydrocele may obscure these organs or the testicle may at times be secondarily involved. Evidence of venereal infection is lacking. There is no history of immediate antecedent gonorrheal urethritis. Urethral discharge if present shows no organisms, or organisms other than gonococci. If bacteriologic diagnosis is impossible, in the presence of acute gonorrheal epididymitis, the complement-fixation test is always positive by the second week of this complication and usually earlier, and by urine culture, gonococci may be isolated. It must be borne in mind, however, that on occasion gonorrheal epididymitis will precede the appearance of urethral discharge or may be synchronous. This betrays a latent posterior urethral infection and in the subsequent discharge gonococci will be found. In this series examination of the urethral smear showed staphylococci 24 times, streptococci 6 times and colon bacilli 9 times.

Acute onset characterizes some cases of tuberculous epididymitis, and at this stage the lesion is clinically indistinguishable from acute nontuberculous epididymitis. Moreover, in the subacute or chronic stage differentiation may be extremely difficult; the error most frequently made is that of diagnosing nontuberculous epididymitis as tuberculous disease. Furthermore, subacute or chronic nongonorrheal nontuberculous epididymitis may be accompanied by scrotal fistulæ, may show beading of the vas, formerly thought to be pathognomonic of tuberculous infection, and palpable changes in the prostate and seminal vesicles may clearly suggest tuberculosis. So important is the correct diagnosis as to both treatment and prognosis, and so difficult is it to make in many instances, that one is best guided by the diagnostic conclusions of Stevens.[2] These are based on a comprehensive clinicohistologic study of a number of cases of these two group types and may be summarized as follows: If the epididymitis is of less than one month duration: (1) Bilateral involvement favors tuberculosis; (2) a previous orchidectomy or epididymectomy almost invariably means tuberculosis; (3) a scrotal sinus of over one month duration is probably tuberculous; (4)

clinical tuberculosis elsewhere in the body means genital tuberculosis in over 90 per cent of such cases. If the swelling is of more than one month duration, rectal examination is of most aid for the older the lesion, the more does definite involvement of the prostate and seminal vesicles point to tuberculosis.

Tuberculin in small doses provokes a local flare-up of tuberculous lesions; nontuberculous disease is unaffected. Recently we have used this method in a series of cases with eminently successful positive results. Minimal doses (0.00001 to 0.00005 cc. old tuberculin) may be given without risk in all cases not showing signs of active pulmonary disease.

Because of its acute onset, torsion of the spermatic cord[3] may closely resemble acute epididymitis. Particularly in those patients showing no evidence of venereal infection is the diagnosis most confusing and is usually made only at operation.

Tumors of the testicle are of more insidious onset, enlarge relatively slower and should be easily differentiated by palpation. On the other hand, we saw a patient presenting an acutely inflamed cryptorchid mass in the lower inguinal canal causing exquisite pain. A urethral discharge was present and contained gonococci. The most likely diagnosis was either acute epididymitis or torsion of an undescended testicle. Operation disclosed a teratoma testis.

Luetic epididymitis is extremely rare and the lesion is primarily an orchitis. Palpation, the Wassermann reaction and antiluetic therapy should establish the correct diagnosis. Syphilitic orchitis (gumma) with associated epididymitis was encountered 4 times in this series.

In the literature we can find no record of death from nongonorrheal nontuberculous epididymitis. Because sterility so frequently ensues, the morbidity is high. Since over 40 per cent of patients who have had bilateral gonorrheal epididymitis are sterile and nongonorrheal nontuberculous epididymes suppurate four times more than gonorrheal, it is presumptive evidence that sterility follows most of the bilateral nongonorrheal nontuberculous infections. The high incidence of secondary suppurative orchitis among the operative cases (30 per cent) lends weight to this assumption.

Treatment. Prophylactically, in the presence of known infection of the posterior urethra, prostate or seminal vesicles, one performs instrumentation or prostatic massage with greatest gentleness and caution. In spite of this care, epididymitis frequently follows. In certain types of operative procedure vasectomy prevents this type of inflammation. Prior to 1925 over 30 per cent of our prostatic patients at Bellevue developed epididymitis at some period of their hospital residence. For the past two years we have routinely performed bilateral vasectomy (ligation with resection of 1 cm. of the vas) with prophylactic success, except in 2 instances.

If the disease is acute on admission the patient is put to bed,

given a cathartic and the adhesive plaster scrotal suspensory devised on the Bellevue Urologic Service is applied.[4] An ice cap locally helps to relieve pain, although some patients are afforded greater comfort by heat. The construction and application of this suspen-

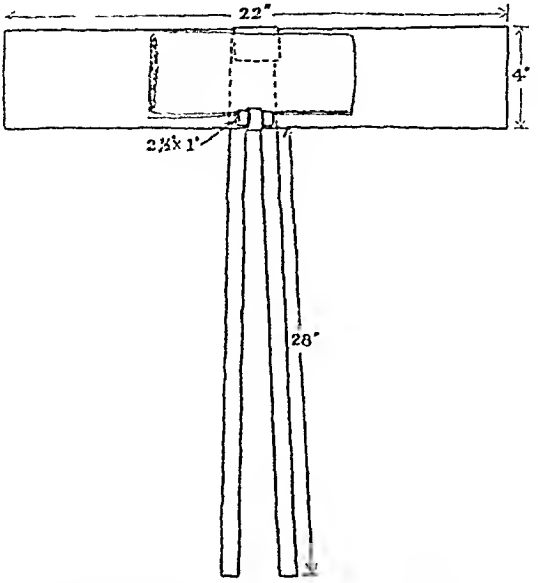

FIG. 1.—Adhesive scrotal suspensory. Note the small perineal roller bandage so essential in the proper construction of this dressing.

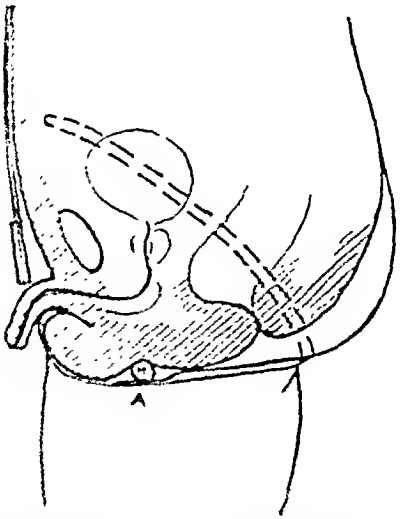

FIG. 2.—Illustrating application of small roller bandage high in the scrotoperineal angle. It prevents scrotal contents from slipping down into perineum.

sory is indicated in Figs. 1 to 4. Its equal cannot be purchased in stores. In many cases pain is relieved at once and in half within twelve hours. Response to treatment is more sluggish in this type than in gonorrheal cases because of the increased incidence of gross suppuration. Those patients unable to sleep because of pain the

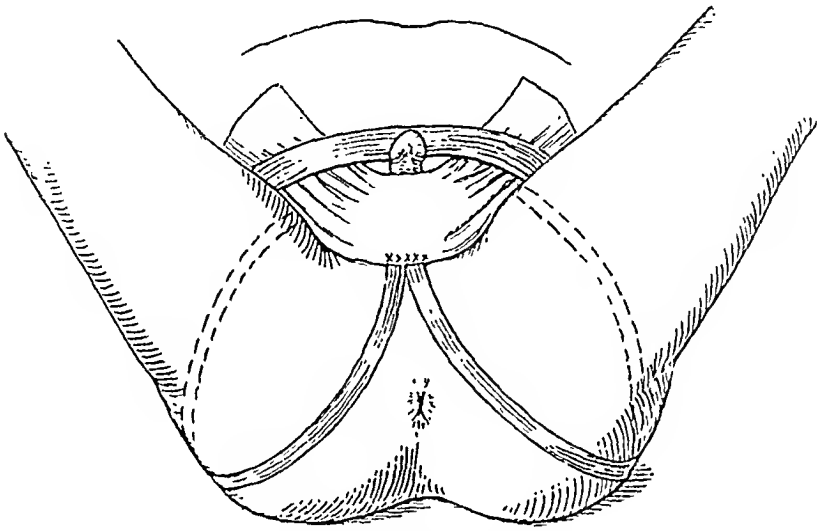

FIG. 3.—Perineal aspect of scrotal suspensory. Small crosses indicate location of roller high in scrotoperineal angle.

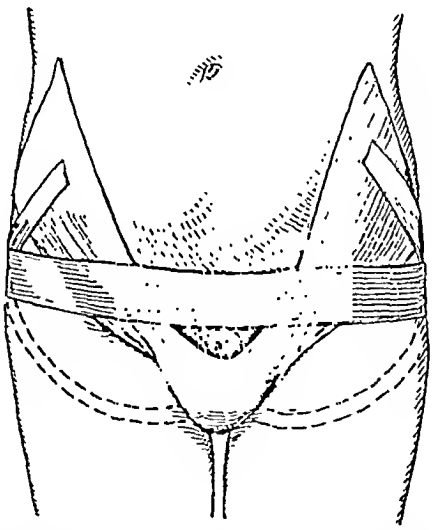

FIG. 4.—Properly applied adhesive scrotal suspensory. The suprapubic cross strap reinforces suspension and affords complete immobilization.

second night after institution of these measures are deemed surgical. If the lesion is unusually acute or grossly suppurating on admission, immediate operation is performed. Most cases of chronic painful epididymitis or those in which there have been several recurrences (or if tuberculosis is suspected) are likewise operated upon. In the

acute type epididymotomy by the method of Hagner[5] is our procedure of choice. Nearly all of the remainder are treated by epididymectomy. Of the 326 cases studied, 79, or about one-fourth, were operated upon. The various types of operations performed are indicated in Table III and from these procedures we have available for microscopic study 54 specimens.

Histologic evidence warrants the assertion that the earlier the epididymis is punctured and drained, the less will suppuration progress. By the same token will tubular destruction and subsequent sterility be minimized. Clinical studies have shown that in gonorrheal epididymitis sterility is not greater after operation but is probably less.

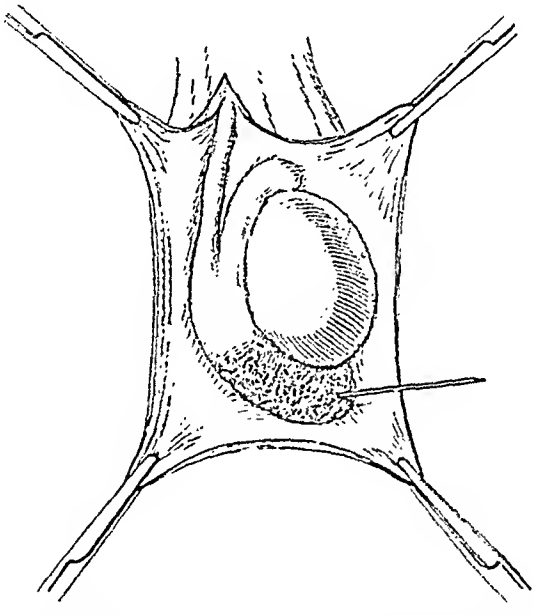

FIG. 5.—Method of epididymotomy (Hagner). Punctures in the epididymis may be made with blunt end of Hagedorn needle.

Following the operative procedure of exposure and multiple puncture of the epididymis according to the method of Hagner (Fig. 5), in certain cases suppuration continues. If moderate, epididymectomy is indicated. We did it twice. If secondary testicular invasion has occurred orchidectomy must be performed. In most subacute and in practically all chronic cases epididymectomy is indicated (Table VI).

The tunica vaginalis is often greatly thickened and indurated, congested if the process is acute, pallid if chronic. Incision of the tunica vaginalis will frequently release hydrocele fluid—sometimes fibrin and, more rarely, serosanguinous exudate (Table IV). If the lesion is of some duration or recurrent, adhesions may be found binding the tunica vaginalis walls together or more firmly uniting

the testicle and epididymis. Old placques of organized fibrin may also be present.

TABLE VI.—SURGICAL TREATMENT.

	No. cases.		No. cases.
Indication:		*Anesthesia:*	
Pain	56	General	52
Abscess	12	Local	36
No indication	25	Spinal	5
	93		93
Type of operation:			
Epididymotomy			22
Epididymectomy:			
Primary			45
After epididymotomy			2
Orchidectomy:			
Primary			16
After epididymotomy			7
After epididymectomy			1
Total			93

TABLE VII.—GROSS PATHOLOGICAL FINDINGS.

		Inflammation.		Hydrocele.	
Part of epididymis.	Abscess.	Acute.	Chronic.	℥ij to ℥ij	
				Clear	13
Head	5	1	..	Cloudy	2
Body	4	1	..	Bloody	2
Tail	12	11	1	Fibrin	4
Universal	8	27	2	Pus	5
Totals	29	40	3		26

TABLE VIII.—PATHOLOGIC HISTOLOGY.

	No. cases.		No. cases.
Acute:		Chronic:	
Exudative	7	Suppurative	13
Suppurative	22	Proliferative	12

TABLE IX.—COMPLICATIONS.

	No. cases.		No. cases.
Abscess testicle:			
After epididymotomy	7	Epididymectomy 6 months after	
After epididymectomy	1	Epididymotomy for pain	1

Greatest involvement is at the globus minor but in this particular type of epididymitis the entire organ is usually universally involved. Abscesses, punctate or grossly confluent, are commonly observed, and in not a few cases will be found penetrating the substance of the testis. The surgical pathology as noted at operation is indicated in Table VII.

A rubber drain is left in all cases for at least twenty-four hours after operation. If considerable suppuration was encountered the drain is left a much longer time. On occasion we have left grossly

infected sloughing wounds wide open to heal by granulation from the depths of the scrotum.

At operation great care must be exercised that all bleeding points are ligated since massive hematomata with deep infection not infrequently follow scrotal operations. Assisting greatly in preventing this complication is the scrotal hemostatic compression bandage also devised on the Bellevue Urologic Service.[4] Figs. 6 to 8 indicate its construction and application. This dressing has practically eliminated scrotal postoperative hemorrhage in our work.

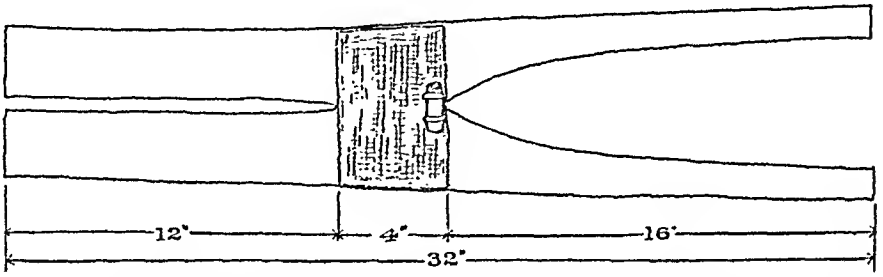

FIG. 6.—Construction of adhesive scrotal hemostatic compression bandage. Note the position of the small roller bandage.

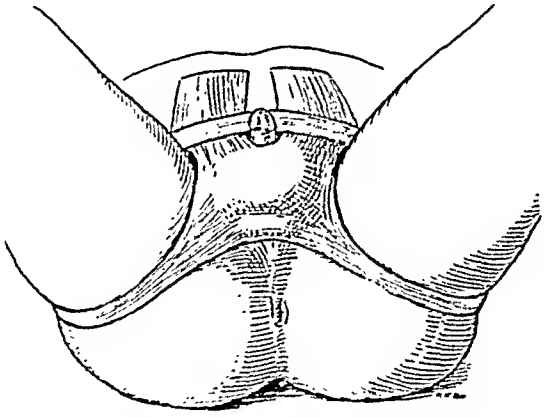

FIG. 7.—Perineal aspect of scrotal compression hemostatic bandage.

Postepididymotomy recurrences are far more frequent in the nonvenereal nontuberculous than in the gonorrheal type of epididymitis and in these cases subsequent epididymectomy must be performed, although orchidectomy is often necessary. In some instances the testicular destruction is aided by collateral inflammatory thrombosis of the spermatic vessels and sloughing of the entire scrotal content of the involved side. Small postoperative hematomata subsequently infected may also assist this suppurative process and unquestionably makes necessary secondary orchidectomy in some patients (Table IX).

Postoperative resolution and resorption is accelerated by the use of the adhesive plaster scrotal suspensory for about ten days. An ordinary scrotal suspensory should then be worn for a month when

all scrotal supports may be discarded. For some time after the acute attack instruments must be withheld from the urethra. Massage of the prostate and seminal vesicles is begun with greatest gentleness and caution. Many patients are best left alone for several weeks with gradual resumption of treatment.

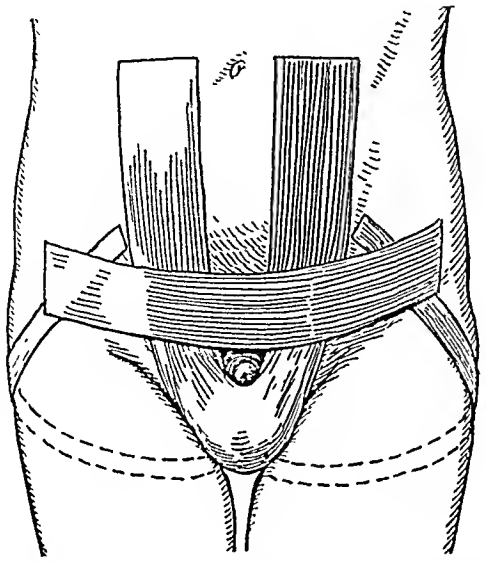

FIG. 8.—Compression bandage properly applied. The parallel straps may be pulled as tight as desired. The cross strap increases the compression and immobilization.

Histopathology. In the acute stage the initial inflammatory process is that pathologically designated as acute catarrhal or exudative. There is cloudy swelling and desquamation of the cylindrical epithelial lining of the tubules with intense leukocytic infiltration of the lumina and interstitial tissues (Fig. 9). As the process intensifies, the tubular basement membranes rupture and confluence of the intratubular and interstitial cellular débris presents the histologic picture of early minute focal abscess (Fig. 10). Polymorphonuclears are the predominant cells in most instances, although occasionally lymphocytes may outnumber. Infiltration by numerous plasma cells, large mononuclears and a variable number of cosinophils with marked vascular dilatation, diapedesis of red blood cells, extensive interstitial edema and, in two-thirds of the cases, hyalin degeneration complete the background of the exudative lesion. Within a few hours many of the microscopic sized abscesses have united and on puncture of the organ at this stage grossly discernible yellowish-white specks of pus may be found. As the lesion becomes older and there is greater tissue destruction, extension and confluence of these small abscesses convert the entire organ into a mass of suppuration (Fig. 11). Even in the face of this destructive onslaught, tissue repair is well under way and about the periphery of the lesions connective-tissue capillary sprouts push their way toward the necrotic centers (Table VIII).

If the organ is not totally destroyed and lost by suppuration, it passes into the chronic stage—the vascular repair processes resorbing dead tissue and laying down new scar. In this manner many tubules totally disappear (Fig. 12), many are left occluded while most of the remaining undergo histologic changes pathognomonic of this stage of the disease. The desquamated cylindrical epithelium is replaced by squamous and by irregular overgrowth coupled with contraction of peritubular sclerosis, the lumina of the tubules present an irregular papillomatous appearance (Fig. 13). In some tissues this overgrowth and contraction nearly occludes the tubules. Throughout the remainder of the organ there is generalized scarring. This is particularly noticeable about the walls of the older blood-vessels. By contraction of this scar certain areas become relatively anemic.

When the inflammation involves the entire organ, as is the rule, few, if any, normal tubules will be found when healing is complete. On the contrary, when only the tail is involved sections taken from the globus major will usually show a preponderance of normal structures. That a third of these patients suffered a recurrence of the disease indicates that obstruction of the vas and certain tubules of the epididymis had not occurred. However, the almost uniform picture of complete tubular destruction or obliteration in the histologic studies of these tissues emphatically indicates the vast importance of early surgical drainage, so that the effect of these destructive processes be minimized.

Summary.—In summary, nongonorrheal nontuberculous epididymitis by virtue of its high morbidity and not infrequent occurrence demands that the nature of the lesion be recognized early and that proper treatment be instituted at once. The invading organisms are predominantly those of the pyogenic variety. While elevation and immobilization of the scrotal contents will care for the majority, about 1 in 4 requires operation and a most liberal surgical attitude must be maintained toward this particular type of epididymitis.

That early and thorough surgical intervention is indicated is proven by the fact that of the 79 cases of this series operated upon, a third eventually lost the testicle by suppuration. Clinical observation shows this is not due to surgical error but rather to the extreme virulence and the pyogenic character of the invading organisms. Without operation in those cases in which surgery is indicated, a still larger number of testicles are sacrificed by suppuration.

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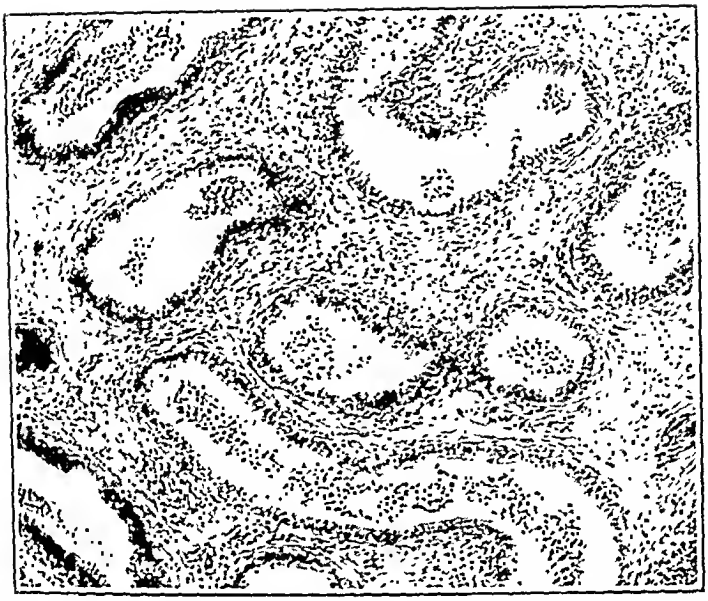

Fig. 9.—Beginning acute exudative epididymitis. Slight intra- and peritubular leukocytic infiltration. The architecture of the organ is well preserved at this stage.

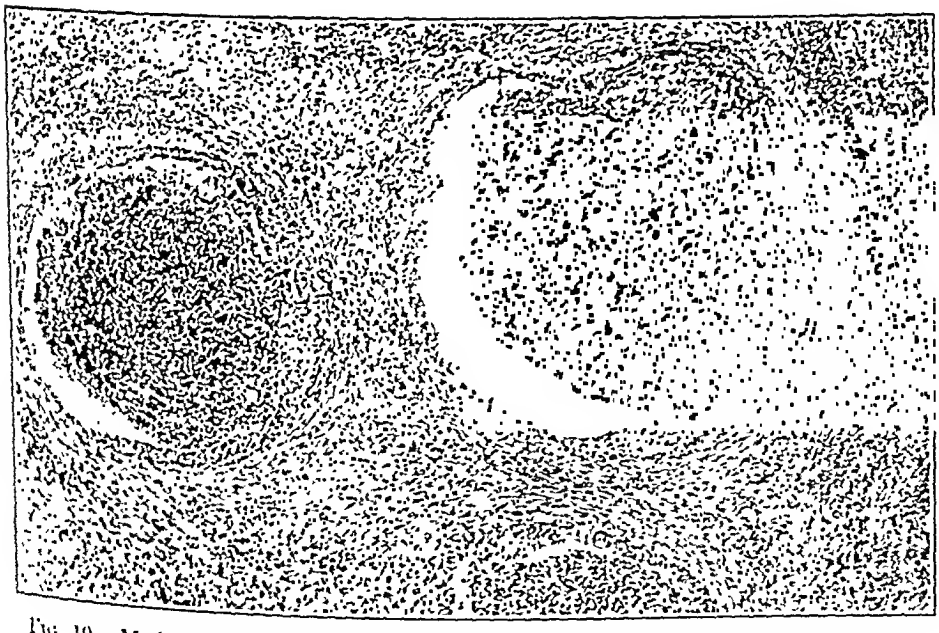

Fig. 10.—Moderately advanced tubular destruction. Rupture of tubule walls and marked peritubular infiltration are noteworthy.

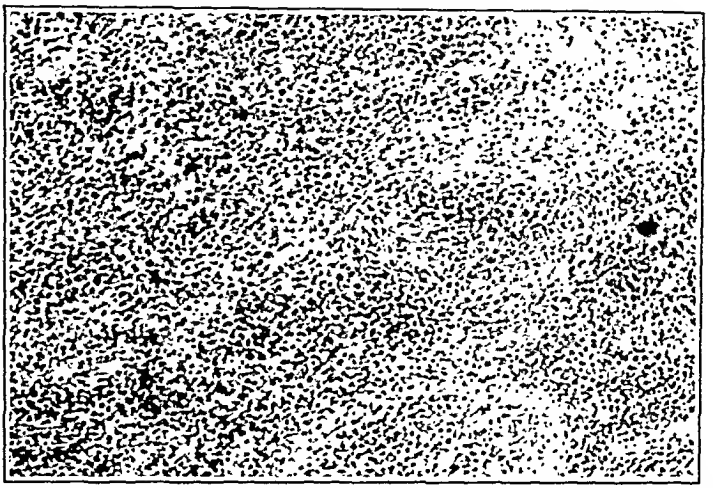

FIG. 11.—Massive necrosis of epididymis. Only a suggestion of the location of former tubules remains.

FIG. 12.—Healing process with generalized scarring of parenchyma and sclerotic obliteration of tubules.

CALCIUM CHLORID IN THE ADJUVANT TREATMENT OF EPIDIDYMITIS.

Some Clinical Observations and Results following the Use of Intravenous Injections.

By Ernest Rupel, M.D.,
INDIANAPOLIS, IND.

Epididymitis is disabling and results in an appreciable economic loss to the patient. Therefore a method of treatment which will diminish these results deserves serious consideration.

An epididymitis is an acute inflammation and its management quite naturally should include those principles of treatment for any acute inflammation; namely, rest for the patient, support or immobilization of, and the proper application of heat—or cold—to the parts affected. Attempts to add to these accepted principles have been made by different observers and this report deals with one such attempt. It is based on the clinical observations made while treating cases of nontuberculous epididymitis, both specific and nonspecific, according to the recognized standards, as compared with the observations made when, to the usual routine, there had been used, as an adjuvant, intravenous injections of aqueous solutions of calcium chlorid. The first group comprises the last 50 cases treated before the calcium chlorid was considered and the last group is made up of the 28 consecutive cases in which the calcium injections were added.

Patients in the first group were first put to bed. They then had an adhesive support applied after the manner described by Collings,[1] had an electric heating pad placed over the support, and were given such medication as their general condition warranted. A review shows that 33 cases were specific in origin and 17 were nonspecific. The shortest period of existence of the epididymitis before treatment was instituted was one day; the longest, twelve; the average 2.34 days. In this series there were five recurrences. Approximately one-half of the patients lay comfortably without any noticeable pain in the testicle within twelve hours after the splinting of the scrotal contents. The standing position, however, provoked decided pain, and there was considerable tenderness on manipulation for two or three days, even if the patient stayed in bed. He must remain in bed these few days to be safest from an immediate recurrence as four, of the five recurrences listed, came in cases that tried to get back to work after only two, and, in one instance, three days. The patients in this group of 50 were confined to bed for a total of two hundred and twenty-eight days, or, for an average of 14.4 days after treatment was begun.

Review of the second group shows that the management was mainly the same as that outlined, the sole exception being that of the addition of an intravenous injection of calcium chlorid. The solutions used were those made by reliable manufacturers and put up in ampules containing 10 cc. of 5 per cent or, sometimes, 10 per cent $CaCl_2.2H_2O$, thus making the usual dose, $\frac{1}{2}$ gm. The injection was made slowly—2 or 3 cc. per minute—while the pulse rate and general well being of the patient was carefully watched. Twenty-two cases were treated in the office and only 6 in the hospital or home. Of the 22, 12 were treated first in the evening, so that they soon had a night's rest in bed after which they were up and gone in the morning without the loss of any time from their vocations. This and other observations are given in Table I. It will be seen that the patients were able to resume their occupations sooner than those that did not receive calcium chlorid.

TABLE I.

Type of organism.	Days duration before treatment.	No. of calcium injections.	Time elapsed before relief was produced.	Incapacity after the first calcium injection, days.	Ambulatory or bed patient during treatment.	Recurrences.
1. Specific	1	2	Over night	0	Ambulatory	0
2. Specific	3	1	1 hour	0	Ambulatory	1 (1 week)
3. Specific	2	1	Over night	0	Ambulatory	1 (1 month)
4. Specific	1	3	Over night	0	Ambulatory	0
5. Specific	1	1	6 hours	0	Ambulatory	0
6. Specific	1	3	Over night	1	Ambulatory	0
7. Specific	1	1	Over night	2	1 day in bed	0
8. Nonspecific	3	2	24 hours	3	In bed 3 days	1 (7 days)
9. Specific	1	1	3 hours	1	Ambulatory	0
10. Nonspecific	1	2	After 2d inj.	0	Ambulatory	0
11. Nonspecific	1	2	Over night	2	In bed 2 days	1 (2 months)
12. Nonspecific	1	2	No relief	10	In bed 10 days	1 (10 days)
13. Nonspecific	1	2	Over night	0	Ambulatory	0
14. Nonspecific	1	4	No relief	14	In bed 10 days	0
15. Nonspecific	1	3	24 hours	5	In bed 3 days	0
16. Specific	4	1	Over night	1	Ambulatory	0
17. Specific	1	2	Over night	1	Ambulatory	0
18. Nonspecific	4	3	2 days	7	In bed 4 days	0
19. Nonspecific	1	3	3 hours	2	See case history	0
20. Nonspecific	30	1	No relief	Indefinite	See case history	0
21. Specific	2	5	24 hours	3	In bed 2 days	0
22. Specific	4	1	Not known	See case history		0
23. Nonspecific	1	3	Over night	0	Ambulatory	0
24. Nonspecific	1	3	Over night	0	Ambulatory	0
25. Nonspecific	2	2	3 hours	1	In bed 1 day	1 (5 days)
26. Nonspecific	1	2	Over night	0	Ambulatory	0
27. Specific	5	3	24 hours	3	In bed 2 days	0
28. Specific	1	3	8 hours	0	Ambulatory	0
Totals	77	62				
Average	2.75	2.2				
Omitting No. 20	1.74	2.2				

A few effects presumably due to the calcium are enumerated in the following brief case notations:

CASE I.—Had an epididymitis on the opposite side two months previous to the present instance. At that time he was confined to bed for three weeks. This time he came to the office in the evening with a fever of 102° and great

pain. He was given a support and 5 cc. of 10 per cent calcium chlorid. He felt no pain the next morning and went to school where he stood on his feet continually. He had no pain afterward.

CASE XII.—Had an epididymitis sixty days following a prostatectomy. There was no noticeable benefit from the injections.

CASE XVIII.—Had a severe attack of bilateral epididymitis for three days. He was in bed, had the adhesive support with heat, but morphin in ½-gr. doses given hypodermically was required to relieve pain until an injection of calcium chlorid was given.

CASE XIX.—Following a prostatectomy, was in bed in a hospital. He developed a fever, then a right epididymitis in the course of eight hours. While the pain, swelling and fever were increasing, an injection of calcium was followed by an immediate fall in temperature and a complete relief from pain and also tenderness.

CASE XX.—Got no benefit from an injection of calcium chlorid. The epididymitis was thought to be tuberculous and was resected, though microscopic examination did not support that diagnosis. The Wassermann test was negative.

CASE XXII.—Received 1 injection, reported that he felt better the next day, and was not heard from afterward.

In Table I it may be seen that the number of specific and non-specific infections is the same, 14. Excluding case 20—a chronic condition—the average number of days the condition existed before treatment was 1.68. This figure is lower than that in the first group, 2.34. The difference is one-half day and is probably not of material difference in the end results. The group of figures "1" shows strikingly well the degree of tolerance that patients have for painful affections in the testicle.

TABLE II.

8 patients	1 injection
9 patients	2 injections
9 patients	3 injections
1 patient	4 injections
1 patient	5 injections

From Table II it can be seen that 8 persons, or approximately 22 per cent of all, received only 1 injection. This is not to be construed as being that number which needed only one injection to effect a cure, for, as in Case XX, no apparent benefit followed the injection and it was not repeated. Case XXII did not return. Some epididymitis cases on the day following the first injection were completely free from pain and remained so for a few days. Then a recurrence of pain made further treatments necessary. It will be noted also in Table II that the greatest number of patients received 2 or 3 injections. These, for the most part, were given at one-day intervals.

In all of the cases the relief from pain was the first sign of benefit. If there was no relief by the next day after the injection, to it was ascribed no benefits even though the patient began to improve the second or third day. Such an improvement was supposed to be due to the other factors in the treatment such as heat, rest, and support which were always used. The striking results were in those patients who never quit work but got immediate and complete relief after a single injection. The fever chart shows the actual rise in temperature with the beginning of an epididymitis following a prostatectomy and shows, also, the response to the administration of calcium chlorid. Swelling subsided slowly much as one would expect inflammatory products to be resolved after an acute attack.

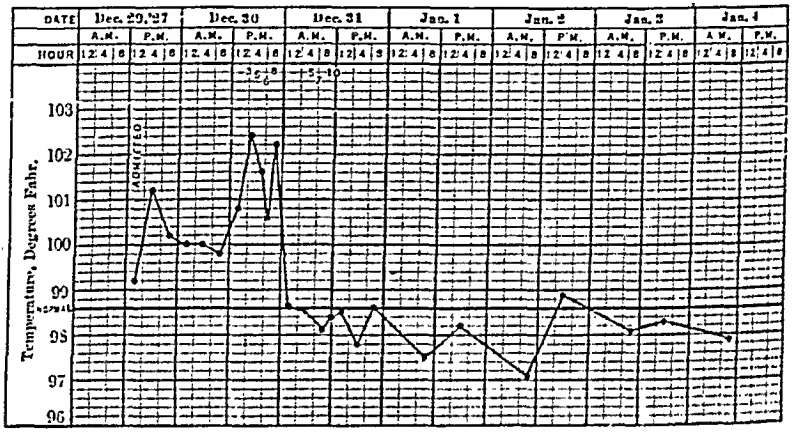

CHART I.

In fairness to the figures tabulating the number of days of incapacity, it should be stated that, with the exception of injections given in the hospital, all the others were given in the office. Those cases marked "ambulatory" were not bed patients. Some went immediately back to bed after the office visit but they were listed as not being ambulatory.

Incapacity and days in bed were considered as one item in the first group. Here there is enough difference to warrant a separate listing since the patients were incapacitated, meaning that they were unable to work—2.07 days. Twelve of the 22 patients seen in the office in the evening felt well enough by morning to get up and go. This was not a common practice when calcium was not added to the routine treatment. Aside from being in bed "over night" the patients in the second group were bed patients for an average of 1.45 days. This is in contrast to the average of 4.14 days in the other group.

It is to be understood here that the cardinal principle of heat, rest, and support were ordered to be followed by the patient. He obeyed until he felt better, enough so that he, of his own accord, discontinued the rest in bed. It is probable that the feeling of well being following 1 or 2 injections should be disregarded insofar as it might limit the total number of treatments.

A clear conception of the reason for many of the clinical results following the introduction of calcium into the system is lacking, though the researches on the biochemistry of calcium are very extensive. Rosler's[2] investigation of the blood picture after the injection of calcium shows an increase in leukocytes and a decrease in blood platelets. Others have substantiated these findings. Baekman[3] and his coworkers noted that the intravenous injection of calcium chlorid induced in rabbits a transient reduction in the number of blood platelets; so did nicotin and atropin. Pilocar-

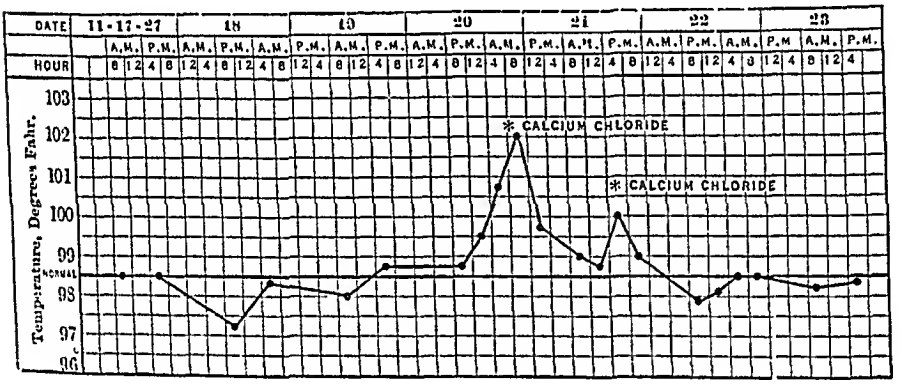

CHART II.

pin and normal salt solution had no effect on the platelets while epinephrin, histamin and acetylcholin increased the number. There is ample evidence to show that the introduction of calcium into the blood stream has a most transient effect on the amount of blood calcium. It was increased 1 to 2.5 mg. per 100 cc. of blood and this increase soon fell to normal—twenty to thirty minutes—in the experiment of Walters and Bowler[4] who gave the calcium chlorid in 1-gm. doses. Koehler[5] found that calcium chlorid ingested over a prolonged period produces an acidosis of the blood pH 7.2 to 7.3.

The toxicity of calcium chlorid when injected into the blood stream in therapeutic doses is apparently *nil*. Walters and Bowler observed no toxic effect on the kidneys either clinically or microscopically. These authors state that the cardiac effect of therapeutic doses is the production of various alterations in the pulse rate. Toxic doses carried out to the limit produce ventricular fibrillation

followed by death of the animal. Locally, the hypodermic administration of calcium chlorid in solutions of 2 per cent, or more, produced necrosis or gangrene in the experiments of Seelig.[6] No evidence of any damage to the veins when injected properly could be found. Without determining a reason for their results, Leff and Spencer[7] showed epididymitis and rheumatism of gonorrheal origin to be favorably influenced by calcium chlorid given intravenously.

Regarding the reasons for the production of the clinical results there can be much speculation. The change in the blood picture can be produced by other drugs, such as atropin and nicotin, without apparent similar effects on an epididymitis. A condition of acidosis is surely not the responsible factor. There is experimental evidence to show that calcium, after intravenous injection, is stored in the tissues. The rapid elimination from the blood makes it quite likely that the determining agent will be found to be the calcium within the tissues, or, perhaps, some new element produced through a tissue change. Whatever the real factors causing the benefit in the clinical condition may be, the factors appear to be more or less transient in their nature. The relief afforded, however, is often obtained quickly and the economic benefit is so great that the use of calcium chlorid intravenously should be considered in the treatment of epididymitis.

Conclusions. 1. Calcium chlorid may be used to advantage in the treatment of epididymitis.

2. It is given in doses of 0.5 to 1 gm. in dilute solutions, intravenously.

3. Relief from pain and tenderness without recurrence is the rule, even if the patient resumes his work daily. Disability, therefore, is greatly lessened.

4. Recurrence of the inflammation often follows too few injections and a course of four or five, once daily, is suggested.

5. No harm from such treatment has been experienced.

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THE CLINICAL ASPECTS OF BRUCELLA MELITENSIS VAR. ABORTUS INFECTION IN MAN.

A Report of the First Cases Recognized in Pennsylvania.

By Richard A. Kern, M.D.,*
PHILADELPHIA, PA.

(From the Medical Division of the Hospital of the University of Pennsylvania.)

Human infection with Brucella melitensis var. abortus assumes an increasing clinical importance, deserving the widest interest in the American medical profession, for these reasons: since the pathogenicity of this organism for man was proven less than four years ago an increasing number of case reports has shown the country-wide distribution of the disease. This is in keeping with the widespread prevalence of the infection in cattle: surveys have shown that up to 90 per cent of herds are infected in some regions, and practically no region is free. For years infectious abortion has been a serious economic problem in the dairy industry. To the objection, "In view of such extensive bovine infection, why so few human cases?"—fewer than 40 are on record—the chief answer is than many cases have been overlooked. These facts are suggestive: of the 36 cases in 20 reports that form the basis of the present discussion, the majority were recognized by laboratory and public health workers and those with a knowledge of tropical diseases, especially Malta fever. Eight of the reporters found 2 or more cases, with a maximum of 6 in one instance. Evans quotes Bassett-Smith to the effect that Malta fever, because of its variety of forms, is seldom recognized in its early stages in the countries in which it is known to be endemic; most of the patients are treated for something else at first. If this is true of Malta fever in its normal habitat, how much more likely will the bovine type of the disease be overlooked in our country where the clinical consciousness of the disease is still on such a low level?

It seems justified, therefore, that the writer put on record 2 additional cases, the first to be recognized in the State of Pennsylvania, one of them undoubtedly arising in that State.

Many of the previous reports of human infection with the abortus organism were made by laboratory workers whose primary interest was not clinical, or who, in view of their own knowledge of Malta fever assumed a similar knowledge on the part of their readers. As a result, many of the case reports are inadequate in clinical description—there are no such data in 14 of the 36 cases. The writer has

* Assistant Professor of Medicine and Lewis Godey Fellow in Clinical Medicine.

therefore gathered all the available clinical information and included it in this review.

Historical. Bruce, in 1893, first described the organism of Malta fever under the name Micrococcus melitensis. Bang, in 1897, described the cause of infectious abortion in cattle under the name Bacillus abortus. Evans, in 1918, showed that these two organisms, hitherto considered wholly unrelated, were so similar as to be indistinguishable morphologically, culturally or even by ordinary agglutination tests. Immune sera for one organism will agglutinate the other, and in such high dilutions that only by special agglutinin absorption tests may the organisms be distinguished. They are really therefore specific varieties of a common genus called Brucella by Meyer and Shaw (in honor of Bruce) and designated by Evans as Brucella melitensis var. melitensis (Bruce) and Brucella melitensis var. abortus (Bang).

Because of the close relationship between the two organisms, Evans suggested the possibility of human infection with the abortus strain from bovine sources. In 1921, Bevan in South Africa reported some cases of undulant fever in patients in whom the only possible means of infection was contact with infected cattle. Sera of patients and cattle both agglutinated the abortus organism in high dilution, but the final proof—recovery of the organism and its identification by agglutinin absorption tests—was lacking. In 1924, Keefer reported the first proven case in a resident of Baltimore, Md., infected by drinking raw cows' milk and from whose blood and urine was recovered an organism that answered all agglutination criteria of Brucella melitensis var. abortus. At about the same time, De Korte recognized a case in South Africa, a man infected while attending an aborting cow. Orpen also reported a case from South Africa in 1924.

Since then, numerous instances of infection from bovine sources have been recognized in various parts of the world. In this country 35 additional cases have been recorded, the majority proven abortus strain infection, the rest in all probability so. In South Africa, Bevan in 1925 was able to collect 35 cases. In Italy there have been several reports of undulant fever from bovine sources: Ficai and Alessandrini observed 16 cases in the village of Arezzo, all from contact with an aborting cow, and 5 cases in another village from a similar cause. Viviani also recorded 2 cases in women who had been in contact with aborting cows. In none of these instances, however, were absorption tests made to prove the organism to be of the abortus strain, and in view of the prevalence of melitensis infection in the goats of the country and its transmissibility to cattle, these cases must remain in doubt. The same objection applies to the case of Giraud in southern France.

Prevalence in America of Abortus Infection in Cattle. There is abundant evidence of the wide-spread occurrence of abortus infection in cattle and of the presence of viable organisms in the milk.

In 1911, Schroeder and Cotton recovered the organism in 8 of 77 samples of market milk tested, and in the milk from 6 of 31 dairies. In 1917, Fleischner and Meyer, as a result of guinea-pig inoculations with certified milk, concluded that "Bacillus abortus, for all practical purposes, is always present in the certified milk produced in the San Francisco Bay regions." Recently Belyea spoke of abortus infection as "wide-spread in the cattle in the Pacific Coast States." Wilson and Nutt, from a study of 488 market samples of cows' milk by guinea-pig inoculation, calculated 5.7 per cent of single milks and 8.8 per cent of mixed milks to be infected. Carpenter and Baker found abortus infection in 9 of 50 herds supplying the city of Ithaca, N. Y.; 60 per cent of the infected cows were eliminating the organisms in the milk. McAlpine and Mickle refer to preliminary surveys in Connecticut showing 90 per cent of the herds to be infected, while only 60 per cent of the milk is pasteurized. In Pennsylvania less than 14 per cent of herds are known to be free of infection (personal communication from State Laboratory of Health).

Data Suggestive of the Probable Prevalence of Human Abortus Infection. There is much important evidence that points to a far greater prevalence of human infection with Brucella abortus than the comparatively few case reports would seem to show. In 1913, Larson and Sedgwick in complement-fixation tests with the sera of 425 children found a more frequent occurrence of antibody for the abortus organism than a positive Wassermann. In 1924, Evans tested 500 sera from various Washington hospitals for abortus agglutinins and found at least one strongly positive (1 to 320); the patient was then found clinically to have the disease. In 1926, Carpenter examined the sera of 20 cases of undiagnosed fevers in New York State: 5 gave a positive agglutination reaction for abortus. Four of the patients were said to be suggestive clinically and one typical of the disease. Hull and Black (1927), in the Division of Laboratories, Illinois State Department of Public Health, did routine abortus agglutination tests on all sera sent in for a Widal test. Of 69 sera from fever cases with a negative Widal, 5 gave positive reactions in dilutions of 1 to 200 or greater, and 1 in 1 to 50. They were able to prove clinically the presence of the disease in 4 of the patients whose sera reacted positively. Hardy (1928), working in the Iowa State Laboratory, examined 783 sera and found 46 positive Widals and 56 positive Brucella agglutinations. He concludes that undulant fever is comparable in importance to typhoid fever in Iowa. Litterer in Tennessee obtained 13 positive abortus agglutinations in 1200 sera submitted for Wassermann tests, an incidence of 1.08 per cent. McAlpine and Mickle in a similar study of 10,157 Wassermann sera in Connecticut found 0.6 per cent to give abortus agglutination in a dilution of 1 to 100.

The Organism. Brucella melitensis var. abortus produces a disease in cattle that usually leads to abortion in pregnant cows. The animals in other respects appear to be healthy as a rule, and not a

few go on to full term in spite of the infection (Sheather). The animals usually abort only once, but occasionally two or three times, then recover from the infection. Many are, however, rendered permanently sterile and so are of no further value except for slaughter. The transmission is usually through food contaminated by infected amniotic fluid and afterbirth. (Six of 9 heifers fed Brucella abortus three times a week aborted.) The organism may perhaps be eliminated in the urine and in this way infect food and bedding. Transmission by coitus also occurs, the infection persisting in bulls as a seminal vesiculitis. Sixty per cent of infected cows eliminate the organisms in the milk, varying in numbers from 500 per cc. to millions per cc., the largest numbers being found just before the drying-up. Suckling calves become infected by the maternal milk, but the infection is only temporary and leads to no degree of immunity (Sheather). The organism is also pathogenic for dogs and swine, in whom a similar disease results.

CULTURAL CHARACTERISTICS. When recovered from human sources, the first generation is hard to grow artificially. Not earlier than the sixth day, blood cultures show a very scant growth: small nonhemolytic grayish colonies of Gram-negative bacilli, 0.5 by 0.5 to 2 microns, nonmotile and not spore-forming. They occur singly or in short chains of two or more. After several subcultures they assume a coccoid morphology. Milk is rendered alkaline but is not coagulated. The organism produces neither acid nor gas in sugar media. It is aërobic, but prefers at first slightly reduced oxygen- and increased CO_2-partial pressures.

RELATION TO OTHER STRAINS OF BRUCELLA. Evans points out that the various strains of the genus brucella are more closely related than the serologic types of meningococcus. A considerable number of strains studied by her fell into 8 serologic groups, 5 of them unimportant and including only 1 or 2 strains. Most of the bovine and porcine strains (33 in number) fell into one large group: Brucella melitensis var. abortus. The next largest group (12 strains) included organisms from caprine, bovine, porcine, and equine sources: Brucella melitensis var. melitensis A. A third group included organisms predominantly of a coccoid type, the original type of Bruce, Brucella melitensis var. melitensis B. The terms para-abortus and para-melitensis have been used to designate minor strains. Organisms from human sources were found to belong variously to all of these. Various methods of nonspecific agglutination have been suggested as a means of differentiating brucella strains, but they have proven unsatisfactory (Ross).

DISTRIBUTION OF BRUCELLA STRAINS IN THE UNITED STATES. Evans identified as var. abortus strains isolated from human sources in Maryland, South Dakota, Connecticut and New York; from bovine sources in Maryland, Wisconsin, Michigan, Minnesota, New York, Connecticut, Iowa and Indiana; from porcine sources in Illinois, Iowa, Missouri and California. Strains of var. melitensis A

from human sources were isolated in Arizona and Texas, from a bovine source in Maryland; from an equine source in Iowa. With the exception of the one Maryland strain, all the var. melitensis strains came from regions in which caprine infection, the source of true Malta fever, prevails. This is especially true of the southwestern states which border on Mexico, and in which the goat-raising industry has assumed large proportions in recent years.

PATHOGENICITY. The question, whether or not Brucella melitensis var. abortus is pathogenic for man, has evoked much discussion. The earlier evidence was in the negative. In France, Nicolle, Burnet and Conseil gave 5 men injections of twenty-four-hour broth cultures of Brucella abortus, 3 bovine and 2 porcine strains, all with negative results. Burnet concluded that "in the countries of epizoötic abortion where man gets undulant fever from contact with the products of abortion, the abortion is caused by a so-called 'abortus,' pathogenic for man: this 'abortus' is really the melitensis: it remains to determine whence it came." Bassett-Smith in England expressed the belief that in the United States a double condition exists in cattle: a true abortus infection and, in the southwestern states, a secondary melitensis infection from Mediterranean goats, and that human cases are probably derived from this secondary source. Ruddock similarly concludes that "all strains of Brucella abortus are not pathogenic to man, only those strains that tend to have melitensis variation." The absence of undulant fever in Germany, where bovine infection exists but not the caprine, has led to similar conclusions.

However, there is sufficient and conclusive evidence in the work of Evans and others that pure strains of var. abortus are pathogenic for man. Numerous abortus strains from human sources have been found here and in South Africa under circumstances where caprine contact and infection of man or cattle seems to have been ruled out. Evans produced abortion in a pregnant heifer with abortus organisms from a human case, and Carpenter caused abortion in 5 heifers, using 5 abortus strains from human sources.

There are, however, wide gaps in our knowledge of the pathogenicity of Brucella abortus. The organism is undoubtedly much less pathogenic for man than is the melitensis variety. The latter is notoriously so: of all organisms it is perhaps the most dangerous for laboratory workers. (If we may credit the newspapers, Evans herself and Keefer have fallen victims to it—Philadelphia *Evening Bulletin*, January 26, 1928.) Laboratory animals show different degrees of susceptibility to abortus infection: the organism is more virulent for guinea pigs than the melitensis variety, but much less so for monkeys, which could resist an abortus dose 1000 times the infective dose of the melitensis organism (Burnet). A similar greater resistance to abortus infection in man probably accounts in part for the lower incidence of undulant fever from this source as contrasted with its occurrence from caprine (melitensis) origin

in subtropical countries. Huddleson points out that Brucella abortus is rarely present in the milk of all the cows of a herd, and, when found, is rarely in numbers over 500 per cc., except at the drying-up period, when many millions per cc. may be found in the milk from an infected udder: such milk could of course heavily infect a milk supply. Evans further suggests that there exists some unknown factor "that prevents undulant fever from becoming such a common disease in temperate climates as it is in subtropical countries."

Clinical Data. This review has been based on: (1) Cases in which the infective agent has been positively identified by agglutinin absorption tests, and (2) cases which, while lacking this final proof, are most probably of abortus origin, as indicated by the specific statement of absence of contact with goats' milk, and the absence of caprine infection in the region. This accounts for the omission of cases from the southwestern states where true Malta fever has been known to exist since Craig's original report in 1903. Holt and Reynolds (1925), in discussing the Malta fever situation along the Mexican border, state that the disease, originally introduced through infected goats from Mexico, has been prevalent for forty years in Texas, and fifteen years in Arizona, is endemic all along the Mexican border, and has increased rapidly with the growth and extension of the goat-raising industry. (American-bred goats are an increasingly important "fur" supply: "unborn kid," "American broad-tail," "American caracul.") Acken's case (Kingston, N. Y.) may well have been a case of abortus infection, but goat contact was not ruled out.

The geographic distribution of the reported cases is shown in the following table:

State (source of infection).	Number of cases.	Reported by.
California	2	Dickson; Ruddock
Connecticut	1	Knowlton
Illinois	4	Hull and Black
Maryland	2	Keefer; Evans
Michigan	7	Huddleson (2) Young (1) Lane (1) Kampmeier (3)
New York	9	Moore and Carpenter (6) Warren, Smith and Linder (2) Fisher and Garen (1)
Ohio	1	Scott and Saphir
Pennsylvania	1	Kern
South Dakota	1	Gage and Gregory
Utah	3	? (cited by Evans)
Virginia	3	Evans Gentry, Cox and Reynolds Kern
Washington	1	Belyea
Ontario, Canada*	1 (?)	Chester and Bailey
Total	36	

* *This patient, a resident of Michigan, drank raw milk while in Canada: no other source of infection found.*

CLINICAL ETIOLOGY. *Sex.* There were 25 males, 7 females; the sex was not stated in 4. The marked male preponderance is due, in part at least, to the mode of infection (see below).

Age. Age figures were available in 22 cases, not stated in 14. The youngest was thirteen years of age; the oldest, sixty-two. The incidence is greatest in young adults, 15 of the 22 cases falling between the ages of fifteen and thirty-five as the accompanying table shows:

Age.	Number of cases.
11 to 15	1
16 to 20	3
21 to 25	4
26 to 30	4
31 to 35	4
36 to 40	2
41 to 45	1
46 to 50	1
51 to 55	0
56 to 60	1
61 to 65	1

Occupation. Occupation plays a definite part in the etiology because of the chance for infection. On farms milk is usually consumed in the raw state, and there is a possibility of contact with the abortion products of cows and hogs, as well as the carcasses of slaughtered infected animals. The last factor is also present in city abattoirs. Laboratory workers may be infected while handling cultures of the organisms.

Of the 27 patients whose occupations were noted, 6 were farmers (3 infected by aborting cows, 1 by hog carcasses), 3 were farmer's wives, and 1 was a tractor manager who spent much of his time on farms. Occupations which gave contact with infected carcasses included 1 butcher, 1 meat inspector (hog careasses only), and 1 histology laboratory technician who went frequently to an abattoir for material (Keefer's patient). There were 2 graduate students in bacteriology (Huddleson's cases) who were working with Brucella abortus, but never handled the melitensis organism. Both of them, however, had been drinking raw milk. The other 12 patients included 2 students and 1 each of the following: private secretary, battery inspector, student nurse, housewife, army officer, golf-course worker, barber, laborer, shipping clerk in a nursery, and a school boy. In the remaining 9, the occupation was not stated.

Place of Residence. Whether the patient lived in a large city, small town or country seemed to be of considerable importance. The records were not always specific, but one could in some infer with reasonable certainty that 2 lived in large cities, 11 in small towns, 10 in the country, 13 undetermined. The likelihood of raw milk consumption in the country and in the small towns is over-

whelming. The importance of abortus infection as a rural health problem is apparent, and will be discussed more fully later.

Source of Infection. Ten patients were known to have used raw infected milk; 9 others used raw milk, but not proven infected. Contact with infected carcasses accounted for 4 cases: 1 farmer. (hog killing), 1 meat inspector (hog carcasses), 1 butcher, and 1 histology laboratory technician. Contact with aborting cows caused 3 cases, all in farmers. There were 2 possible laboratory infections (raw milk infection not ruled out). No data were available in 10 cases.

Other possible sources must be considered. The organism is infective for dogs: Van Saceghem in the Belgian Congo noted that at a time when cows aborted, abortion was also observed in dogs. The dog serum proved to have a positive agglutination reaction for Brucella abortus. Human infection with Malta fever from canine sources has been observed in Europe. Sheep may carry the infection. Other recognized modes of transmission of Brucella melitensis var. melitensis, such as mothers' milk and intercourse, should be kept in mind as possibly active in the spread of abortus infection.

Clinical Picture. There is no characteristic clinical picture of abortus infection. Clinically indistinguishable from its twin, Malta fever, it must, like that disease, be described as an infection with an irregular course and an indefinite duration. This extreme variability and the simulation of half a dozen other diseases probably account for a frequent lack of its recognition. This variability of the disease cannot be too greatly stressed: Few physicians in this country, especially in the more northern sections, have ever seen a case of Malta fever. They either have no conception of the disease at all, or they remember vaguely that Malta fever is also called undulant fever because, they think, of its "characteristic" undulant fever curve. A perusal of the varied disease pictures presented by even this small series of cases will serve to convince the reader of the futility of attempting to diagnose the disease on a clinical basis alone. What is needed is a wide-spread clinical consciousness of the disease, a high index of clinical suspicion, that will lead physicians to ask routinely for an abortus agglutination test in all cases of undiagnosed fever.

Incubation Period. No data are available: it may be like that of Malta fever, in which an incubation period of six to fourteen days has been described.

Mode of Onset. The onset was vague and gradual in 17, sudden in 6, not stated in 13. Intercurrent factors may precipitate a sudden onset, or give rise to a sudden exacerbation of a mild infection: one of Warren, Smith and Linder's cases, a student nurse, had a sudden onset of illness following a dose of typhoid vaccine. In one of the writer's cases a mild fever rose suddenly to 105° F. immediately after general anesthesia and tonsillectomy.

*Onset Symptoms.** The commonest onset symptoms are those of a vague general infection. Fever (16) is the most frequent initial complaint: the patient becomes vaguely conscious of an afternoon or evening rise of temperature, gradually increasing in degree and with attendant symptoms variously described as malaise (8), weakness (5) or "tired feeling" (3); at times with headache (7), bilateral, frontal or occipital. There may also be aching muscular pains (4), generalized or in the back and extremities. Chilliness (3) and sweats (5) may be present, are usually nocturnal and the sweating may increase rapidly to be described as "drenching." Frank chills (6), fever and sweats are more likely to usher in a sudden onset.

Early gastrointestinal symptoms are less frequent: there have been observed nausea (3), vomiting (1), anorexia (3), "gastric disturbances" (1), epigastric pain and distress (1), diarrhea (1) and sore teeth (1).

Occasional initial symptoms are slight sore throat (3), cough and hoarseness (1), nervousness (1), and insomnia (1). One patient first noticed loss of weight, and another soreness and lameness in one hip.

Further Course. There is nothing characteristic. Some patients become increasingly more ill and soon seek medical aid. Others are not much disturbed by the illness: in spite of a considerable degree of fever, they may not be bedfast more than a fraction of the duration of the disease, or they may be wholly ambulatory (2). One of Huddleson's patients, a graduate student in bacteriology whose illness lasted over eight months, continued at his work in spite of weakness, sweats, and fever at times reaching 103°. From time to time he consulted various physicians, none of whom recognized the nature of his disease. Finally, after symptoms had been present at least six or seven months, he diagnosed his own case after reading some case reports of abortus infection. One gets the impression rather generally that the patients are subjectively not so ill as their appearance and fever would seem to warrant.

The only universally present symptom is fever, but there is no characteristic curve. It may be one continued curve, or there may be waves of pyrexia with intervening afebrile periods. The continued fevers may be sustained, or remittent to the degree of simulating a septic or malarial fever. In either type, continued or undulant, the temperature tends to be low in the morning and up in the evening, climbing at first in a succession of "spikes" of increasing height, while defervescence takes place by reversing this process in lysis.

Information concerning the fever was available in 21 cases. In 12 of these the fever was continued; in 2 instances it was described as sustained, "typhoid-like," but daily fluctuations of several degrees

* Figures in parentheses refer to the number of cases showing a given symptom, sign, and so forth.

are much more common. The duration of the continued fevers varied from ten days to several months. Two patients with the continued type of fever suffered a short relapse, the one lasting two days and coming twelve days after a thirty-seven-day continued fever. A continued-fever curve may show a tendency to undulation without there being actual afebrile periods.

An undulant temperature curve was observed in 9 patients. There was no constant duration of fever waves or of the afebrile intervals, nor any constant number of undulations. Fever waves numbered from two to a long succession over a series of months; they lasted from two to twenty days and came at intervals of from two to twelve days. In 2 of these 9 patients an initial undulant curve gave way later to a continued fever, sustained in one and remittent in the other.

The highest temperature recorded in 1 case was 105.4° F.; in 4 patients the fever reached between 104° and 105°; in 6 others, 103° to 104°; in 2, the maximum was between 102° and 103.° No figures were available in 23 instances.

Pulse and respirations were found elevated in proportion to the temperature rise, although in one patient "tachycardia" was noted, this in the absence of other cardiac pathology. The pulse occasionally lagged a little below the temperature (Griffith graphic chart), but no instances of true bradycardia were noted.

Orpen, in his discussion of 35 cases of abortus infection in South Africa, expresses the opinion that the fever curves are more variable than in true Malta fever. Viviani found the fever in his Italian patients to be of the continued type more often than is usual in Malta fever, and Ficai and Alessandrini also report less undulation of temperature in their suspected abortus cases.

Drenching sweats (11) (in one instance said to be of a "peculiar odor") are very frequent. Usually nocturnal, they recur night after night for weeks, and commonly follow frank chills (8).

Nervous symptoms are probably next most frequent. The patients complained variously of headache (4), insomnia (3), "irritability" (2), nervousness (1), restlessness (1) and dizziness (1). One was described as "introspective," and another as "drowsy, apathetic." Delirium, "mild," was noted only once.

Gastrointestinal symptoms were less marked in the *fastigium* than in the onset. They included anorexia (6), constipation (3), diarrhea (2), alternate constipation and diarrhea (2), "gastric disturbances" (1). In one patient anorexia yielded later to a ravenous appetite: the patient would hurriedly bolt the food brought him out of fear lest the tray be removed before it was empty. On several occasions he stuffed himself until he had to vomit to get relief.

Pain over the spleen was complained of by 2 patients, one of them a patient with endocarditis and splenic infarction.

Respiratory symptoms were infrequent and mild: slight epistaxis (1), "sense of oppression and suffocation" (1), chest pain (1), "continual cough" (1). In the last patient Roentgen ray of the chest showed "peribronchial thickening."

Of much interest are the joint symptoms. Five patients had joint pains: ankles and knees (1), right hip (1), left hip and lumbar vertebræ (1), both hips and knees (1), no description (1). In 1 patient the joints were swollen as well as painful. Two were thought to have acute rheumatic fever, and 1 was treated for two weeks with full doses of salicylates but obtained no relief. In an unreported case of which the writer has knowledge (Johns Hopkins Hospital) undulant fever was associated with an intermittent hydrarthrosis.

Scattered symptoms included burning on urination (1), "weak eye-sight" (1), palpitation (1) and embolic phenomena (hemiplegia, splenic infection) (1), the last in a patient with endocarditis. In 1 patient, a lactating woman whose infection began a few weeks after parturition, each three- to five-day wave of fever was attended by a menstrual flow of the same duration.

General complaints of common occurrence were loss of weight (8), up to 30 pounds in some and warranting the term "emaciation" in several; weakness (4), prostration (1).

Attention is called at this time to certain other symptoms and clinical manifestations not noted in the American cases but observed in abortus cases elsewhere, or in Malta fever and therefore likely to occur also in abortus infection. A patient of Bevan's with the abortus disease had seminal vesiculitis with blood-stained semen. This corresponds to the similar involvement of bulls and leads to speculation on the possibility of transmission by coitus, as well as the part which Brucella abortus may play in human abortion. Abortion has been noted in Malta fever but is apparently not a common event, nor do infected goats tend to abort. There have been reports of farmers' wives who aborted at a time when infectious abortion was prevalent in their herds, but no such cases have been subjected to investigation and proof of abortus infection. Williams and Kolmer, seeking information on this point, examined the sera of 50 women who had aborted. Complement-fixation tests, using an abortus antigen, were not more frequently positive than the Wassermann reaction. Agglutination tests with 12 sera were negative. Orchitis, mastitis, sciatica and other forms of neuritis have been observed in Malta fever but not, as yet, in human abortus infection.

Physical Examination. This is usually negative except at times for evidences of a prolonged infection (emaciation, secondary anemia), moderate enlargement of spleen and liver in a third of the cases, and joint involvement in half that number. In 5 patients the physical examination was entirely negative..

Skin rashes were observed in 4 patients. Rudduck's patient had crops of petechiæ after each wave of fever. One of Moore and Carpenter's patients showed red edematous spots, 2 by 3 inches, over the inner malleoli and over the heads of the tibiæ. One patient had a few reddish scaly spots on the front of the chest and abdomen. A few lesions like rose spots were found in one of the writer's cases.

The chest is commonly negative. A "few râles" were found in one instance, another patient had a systolic murmur at the pulmonic area and a third had the signs of a mitral stenosis and an aortic valvulitis.

The abdomen in 1 patient showed slight general tenderness; there was tenderness in both hypochondria in 1, 2 patients had tenderness over an enlarged spleen, and in 1, tenderness over the gall bladder and an enlarged liver was present. In 21 patients, the spleen was palpable in 8, not palpable in 13. The enlargement was not great, the organ reaching only 1 or 2 cm. below the rib margin. The liver was palpable a finger's breadth or so below the costal margin in 6 and not palpable in 11 of 17 patients. Jaundice was never observed clinically but Keefer's patient showed a transient urobilinuria.

Joint involvement was noted in 5 of 15 instances, 1 with swelling, pain and tenderness, the rest without swelling. The joints affected have been referred to.

Adenopathy was present in 2 of Kampmeier's cases. In 1 patient the lymph nodes were generally enlarged, "pea to nut" size; in the other the cervical glands alone were involved. Whether or not the adenopathy cleared up subsequently was not recorded.

Blood-pressure readings were recorded in 6 patients and were all low normal: systolic pressure, 104 to 110 in 4 cases, 118 and 120 in the other 2; diastolic pressure 65 to 70.

Dicrotic pulse was noted in 1 patient.

Duration. The duration shows very well the failure of the disease to conform to any type. In 21 of the patients (no data in 15) the length of illness varied from ten days to over ten months. One died after a "long illness." (Malta fever is said to last from two weeks to two years.) It is difficult to give exact figures for the patients in this series, partly because of the vagueness of the time of onset, partly because some of the patients were still ill at the time of the report. Approximate figures are given in the following table:

Duration.	Number of cases.	Duration.	Number of cases.
10 days	1	10 weeks +	1
12 days	1	11 weeks +	1
3 weeks +	2	3 months +	2
5 weeks +	1	6 months +	1
6 weeks +	2	8 months +	1
7 weeks +	3	10 months +	1
8 weeks +	3		

Termination. Died, 2; cured, 14. Not stated or disease still active, 20. The deaths occurred, the one in a man aged twenty-one years with an associated active endocarditis (Scott and Saphir) after an illness of many months, the other in a man, aged forty-one years, who "died after a long illness," details lacking (Moore and Carpenter). The mortality for this series was 5.5 per cent. The mortality of Malta fever has been given as 2 to 3 per cent, and up to 14.3 per cent in certain epidemics (Goglia), the deaths tending to be in the debilitated: cardiacs, luetics, the tuberculous, and the like. These mortality figures are probably much too high because of the mild cases, perhaps quite numerous, which never come under observation.

Pathology. MORBID ANATOMY. The human material is meager. Moore and Carpenter's patient showed "septic splenomegaly" at necropsy; the other findings were not given. The case of Scott and Saphir is here given in some detail because of the associated active endocarditis.

The patient, a laborer, aged twenty-one years, with a past history of rheumatic fever at thirteen and again at nineteen years, was under observation for three periods from December, 1925, to the time of his death in September, 1926. The disease picture included fever, chills, the evidences of mitral stenosis, slight splenic enlargement, eventually embolic phenomena (hemiplegia, pain over the spleen). Blood culture yielded the Brucella abortus, identity proven by absorption tests, and the serum agglutination reaction was positive in 1 to 1000 dilution. The leukocyte count was 20,000. At no time were streptococci found in the blood. *Necropsy.* The heart weighed 550 gm.; there was an old mitral stenosis, and numerous soft grayish friable vegetations were present on the mitral and aortic valves. No Aschoff bodies were found. The heart's blood again yielded the abortus organism but no streptococci. The spleen (950 gm.) showed recent infarctions and perisplenic adhesions. The liver (2150 gm.) showed cloudy swelling and passive congestion. There were pleural adhesions and some effusion. The serosa showed petechiæ. No source of any other infection was found. There was no actual proof that the abortus organism was responsible for the recent endocarditis, and the case was reported as "one of acute and chronic endocarditis associated with Brucella melitensis (abortus) bacteremia."

Scott and Saphir refer to 4 cases reported by Hughes of endocarditis caused by Brucella melitensis and to Lagriffoul, Arnal and Sardon's case of endocarditis in Malta fever.

CLINICAL PATHOLOGY. *Blood Count.* The blood findings are essentially a slight to moderate secondary anemia, color index less than one, and a subnormal or normal leukocyte count.

Red cell counts were given in 12 patients. In 5 the counts were

normal; in 3, from 4 to 5 million; in 3, from 3 to 4 million; one count fell below 3 million (2,800,000).

Leukocyte figures were given in 18 cases. In 5 all were normal (6 to 10,000); 11 had counts under 6000 on one or more occasions, while 8 showed figures under 5000. The lowest counts were 2200 (Belyea) and 2400 (Moore and Carpenter). Four showed a leukocytosis: one of 20,000 (endocarditis, only one count given), another 15,000 (only one count given), a third with an initial count of 12,000 and then several normal figures; a fourth, 17,000 after anesthesia and tonsillectomy, with a subsequent leukopenia.

The differential leukocyte picture showed most commonly a low neutrophil percentage and a relative lymphocytosis in the presence of leukopenia. The lowest neutrophil figure was 22 per cent; the highest lymphocyte, 62 per cent. Monocytes were normal except for one report of 22 per cent, with other normal counts in the same patient. The eosinophils were normal, only twice reaching 3 per cent, the remaining figures 1 per cent or less. The basophils were normal: 0.1 to 1 per cent.

Blood Culture. This was reported in 20 cases: in 10 (50 per cent) one or more positive cultures were obtained; in 10 patients 1 to 4 cultures in each remained sterile. The earliest positive was on the sixth day of the disease. In Keefer's patient a series of positive cultures was obtained over a period of sixty-seven days, the last one a week after the temperature had fallen to normal. In 1 case (Moore and Carpenter) blood cultures were positive before, and negative after, the first intravenous injection of mercurochrome. In 1 patient (Moore and Carpenter) both Brucella abortus and Bacillus typhosus were found in the blood. In Malta fever the blood culture is positive in 65 per cent of cases (Goglia).

Agglutination Tests. There is no evidence in this series of cases to show how early agglutinins for Brucella abortus appear in the blood. Tests were not made early in the disease because for some time the nature of the infection was not suspected. In all the reported cases (data in 22) even the earliest tests seem to have been positive or very suggestive. (In melitensis infection agglutinins are said to be present as early as the fifth day.) The agglutinin titer rose to variable heights in the course of the disease, tended to fall more or less rapidly after defervescence, fell somewhat in afebrile periods between undulations, and remained positive for months after cure. The titer varied widely in different patients: the highest was in Keefer's patient (agglutination of the organism obtained from the patient's blood by his own serum in a dilution of 1 to 20,480); the lowest, 1 to 30, in a patient whose blood yielded a proven strain of Brucella abortus. The maximum agglutinin-titer figures are tabulated for the 22 cases, as well as titers for Brucella melitensis in the cases in which tested for:

Dilution.	Number of cases.	Titer for Brucella melitensis.
1 to 20,480	1	1 to 5120
1 to 10,000	1	1 to 1500
1 to 5,120	1	
1 to 5,000	1	
1 to 1,280	2	
1 to 1,200	1	1 to 1000
1 to 1,000	2	
1 to 960	1	
1 to 640	1	
1 to 500	3	
1 to 400	2	1 to 135 (1 case)
1 to 320	3	
1 to 200	1	
1 to 80	1	
1 to 30	1	

In Keefer's patient the titer fell from a maximum of 1 to 20,480 during the disease to 1 to 320 four months after recovery. In another patient whose serum gave a 1 to 400 positive during illness, the titer fell to 1 to 50 two months after recovery. In one of the writer's cases with a maximum titer of 1 to 5120 the figure was 1 to 640 a week after defervescence; in the other the figure during a wave of fever was 1 to 640, and in an afebrile interval, 1 to 320.

Keefer observed in his case a negative pre-agglutinoid zone that may figure in the diagnostic problem: while strongly positive in higher dilutions (up to 20,480) the patient's serum gave negative reactions with the organism cultured from his own blood in dilutions from 1 to 10 up to 1 to 160. The nature of this negative pre-agglutinoid zone is unknown. Observed also in the case of other organisms, it seems to be more pronounced in the case of Brucella. It is most marked when recently isolated organisms are employed; it disappears when the organisms have been kept in the ice box for a week.

Agglutinin Titer and Prognosis. It has been claimed that in Malta fever the serum agglutinin content bears a relation to prognosis, the higher the titer the better the chance for recovery. This series of cases gives little information on this point: the one fatal case (endocarditis) had a positive agglutination test in 1 to 1000 dilution; no figures were available in the other. The patients with the lowest titers recovered.

Immunity. There is no evidence as to the duration or degree of immunity conferred by abortus infection. In Malta fever, some have claimed, others denied, that one attack protects permanently against reinfection.

Cross-agglutination Tests. Francis and Evans have shown that the sera of patients with melitensis infection, with abortus infection and with tularemia possess cross-agglutinins in varying amounts, each for the other two organisms. (This will be discussed more fully later.) In 2 of the patients of this series such tests were made. In Rudduck's case there was a negative test with Bacterium

tularense. With the serum of one of Warren, Smith and Linder's cases, a student nurse whose illness was precipitated by the second injection of typhoid vaccine, the following agglutinin titers were obtained: Brucella abortus, 1 to 20, 1 to 1500, 1 to 10,000, 1 to 3600; Brucella melitensis, 1 to 20, 1 to 1500; Bacterium tularense, 1 to 160; Bacillus typhosus, 1 to 80. Their other patient, in addition to a maximal figure of 1 to 5000 with Brucella abortus, had an agglutination titer of 1 to 40 for Bacillus typhosus. In the first instance, the typhoid vaccine may account for the positive Widal; there is no available explanation for the second case. Widal reactions in 15 other patients were negative on from 1 to 4 observations.

URINE. *Routine Analysis.* Reports in 13 cases were available. The examination was negative in 6. A trace of albumin was found in 4. Two of Moore and Carpenter's cases showed glycosuria ("1 per cent;" "trace"). No information was given as to its possible previous presence or subsequent course in these patients. Urobilinuria was observed in one instance. Casts were found in 4 instances: a moderate number of various types in 1, occasional casts in 3, with a negative urine noted in 1 of the last on discharge. Alkaline urine, with phosphaturia, was constantly present in 1 of the writer's cases. Pyuria was present in 1 instance.

Urine Culture. In the 8 instances in which urine culture results are available, Brucella abortus was recovered in 2 patients. Cultures were negative in 6 cases (twice in 2).

Other Laboratory Data. The blood Wassermann was negative in the 9 sera examined. The blood urea nitrogen was 14 mg. per 100 cc. in 1 instance. The basal metabolic rate in 1 patient with an enlarged thyroid (Michigan) was +27 per cent during the illness (febrile) and +7 per cent during convalescence.

Diagnosis. In writing of Malta fever twenty-five years ago Craig said: "There are no pathognomonic symptoms of Malta fever. The symptoms observed are so inconstant and confusing that no one can be said to be typical of the disease. A differential diagnosis is almost impossible in the majority of cases without the aid of the microscope and the serum test." The diagnostic problem of brucella infection is eminently a laboratory one. Its only solution lies in the routine use of the proper tests in all undiagnosed fevers. Hardy has suggested that, until physicians generally are cognizant of the disease, state and municipal laboratories should test all sera, sent for Widals, for the brucella as well. This is already being done to a considerable extent in many places. But very few hospital laboratories have as yet taken up the test: there is opportunity for much missionary work in this direction.

Two diagnostic procedures are essential: (1) Blood culture and (2) serum agglutination tests.

Blood Culture Technique. Evans recommends the following procedure: Take the blood (15 cc.) at the height of a pyrexial wave.

Plant some at once in flasks containing 30 cc. of infusion broth, varying the inoculum: 0.1 cc., 0.2 cc., 0.5 cc., and 1 cc. per flask. The rest of the blood is divided into 2 sterile test tubes. After the serum separates, remove and save for agglutination tests. Plant each clot in a flask with 50 cc. of infusion broth: by the removal of antibodies (serum) one might get a growth when none occurs in whole blood cultures. Examine cultures from the fourth to the tenth day (cultures are rarely positive under six days and may take much longer); each time make subcultures on infusion-agar slants with 2 or 3 cc. of broth from the bottom of each flask to each agar slant and for two or three hours place the tubes so in the incubator that the broth covers the slant. The abortus variety grows best under an increased CO_2 tension (10 per cent by volume) (Theobald Smith.) The organism appears on agar in small "dew-drop" colonies.

Urine Culture. (Evans.) Collect under sterile preeautions, let flow over infusion agar, then layer. Let stand for seven or eight days. Glucose agar may enhance the growth of melitensis, but also that of contaminants.

Serum Agglutination Test Technique. (Evans.) Brucella abortus alone is quite satisfactory for routine testing for brucella infection. The antigen is prepared as follows: the organism is grown on glucose agar (PH 6.8) in Blake bottles. Each bottle is seeded with the growth from a glucose agar slant in 2 cc. of physiological saline solution. Incubate the bottles for forty-eight hours. The organisms must be killed by heat before removing from the agar. To do this add 25 cc. of salt solution, heat in a water bath at 65° C. for one-half hour. After the agar cools, emulsify the growth in the salt solution by agitating (carefully, not to break the agar). The suspensions are then put in centrifuge tubes and 25 cc. more of salt solution are added to the growth from each bottle. Smears should be prepared from the suspensions and examined microscopically to insure purity. Centrifuge, pour off the supernatant fluid, and emulsify the sediment in a few cubic centimeters of saline, denser than is desired for stock. Then adjust the stock using the turbidity standard (described in Standard Methods of Water Analysis, American Public Health Association). *Standard:* dry Pear's precipitated fuller's earth and sift through a 200-mesh sieve. One gram in 1 liter of distilled water equals turbidity 1000. A silica standard, turbidity 300, sealed in a glass vial 16 mm. in diameter and of 10-cc. capacity, has been found best: ordinary type is just legible through it. Place 0.1 cc. of the dense bacterial suspension in an empty vial and add water until the turbidity matches the standard. Then adjust the stock to turbidity 20,000. If serum is to be sent to a distant laboratory, preservative should be added: 50 per cent glycerin is best. Phenol or tricresol should not be used in a concentration of over 0.2 per cent.

The test is carried out in tubes 1 by 7.5 cm. Prepare serum dilutions with saline, 1 to 10, 1 to 20, 1 to 40, and so forth, and place 0.5-cc. amounts of the various dilutions in the tubes; add 0.5 cc. of the antigen, turbidity 1000, to each tube. The final turbidity is therefore 500. Incubate at 55° C. in a water bath for four hours, then place in the ice box and read the next day. The reading is in degrees of turbidity: "4," complete; "3," 75 per cent; "2," 50 per cent; "1," 25 per cent; fresh standards "3," "2," and "1" are made up every day that readings are made, using the serum-antigen mixture from tubes in which no sediment is present.

What Agglutinin Titer is Positive Evidence of Infection? Known cases of melitensis infection (proven by positive blood culture) have shown a titer as low as 1 to 10. The lowest titer in a proven case in this series of abortus cases was 1 to 30. A negative reaction must not be considered certain evidence against infection. Evans believes that complete agglutination in 1 to 40 or lower is suspicious, and in higher than 1 to 40 is good evidence of brucella infection, past or present. Others set 1 to 200 as the minimal convincing positive titer. Evans feels it is probably a matter of technique standards: the density of antigen used is probably the greatest source of error.

These figures may be compared with those of Goglia for Malta fever: he considers a titer of 1 to 150 as practically always indicative of infection, and highly suggestive at 1 to 50. The agglutinins in Malta fever may reach a titer as high as 1,300,000 (Eyre), and persist at a level of 1 to 50 or more for a year and upward: four years (Roger and Lagriffoul), ten years in 1 case (Eyre).

Cross Agglutinins. Francis and Evans, in a study of 100 human tularemia sera, found 37 to contain cross agglutinins for Brucella melitensis and Brucella abortus, which in 3 instances reached the same titer for both of these organisms as for Bacterium tularense. Anti-tularense sera of rabbit, sheep, horse and rooster all cross-agglutinated Brucella melitensis and Brucella abortus, but as a rule in lower dilutions. Three of 8 human brucella-infection sera cross agglutinated the tularemia organism, but in a slight degree; the rest contained no cross agglutinins. Anti-tularense sera, after absorption by Bacterium tularense, had no agglutinins left; after absorption by Brucella abortus, had no agglutinins left for abortus but still agglutinated tularense in the original titer; after absorption by melitensis, had no agglutinins left for melitensis, retained their original titer for tularense, and gave variable results with abortus. They conclude that sera of patients suspected of tularemia or brucella infection should be tested for agglutinins of both organisms, unless the history shows a recognized source of tularense infection. If the difference in titer is marked, the diagnosis is obvious; if the titers are the same or nearly so, agglutinin absorption tests must be resorted to.

Cross agglutinins for other organisms (Bacillus typhosus) may be

ignored: if there is any doubt, such other agglutinins may be destroyed by heating the serum to 56° C. for thirty minutes (Evans).

Diagnosis by Skin Test. Burnet has claimed that in Malta fever the intracutaneous injection of 0.1 cc. of a Berkefeld filtrate of a broth culture of Brucella melitensis will give a positive skin test that begins in six to eight hours and lasts for several days. Other workers, however, have cast doubt upon the specificity of the reaction. The test has not been tried in abortus cases.

Differential Diagnosis. Brucella infection very strikingly simulates other diseases, and consequently erroneous diagnoses are common. In this series the admitted mistaken diagnoses were frequent, and the many diagnostic tests applied (chest roentgenogram, Widal, search for malarial plasmodia, and so forth) point to still more. The cases were variously diagnosed:

Tuberculosis (6)—Prolonged illness with fever, night sweats, weakness, emaciation, blood count.

Subacute Bacterial Endocarditis (4)—Fever, chills, sweats, weakness, emaciation, blood count, enlarged spleen, and in 1 case, petechiæ.

Typhoid Fever (3)—Continued fever, negative physical findings except for the enlarged spleen, leukopenia. (Typhoid was probably suspected more often than in 3 patients: Widals were performed in 17 cases.)

Rheumatic Fever (2)—Fever, sweats, joint involvement.

Malaria (2)—Chills, fever, sweats, enlarged spleen.

Pelvic Inflammation (1)—In Ruddock's case the disease began a few weeks postpartum.

Influenza (1).

In each instance specific tests corrected the diagnosis.

Treatment. The treatment was largely symptomatic. One patient seemed to get well after quinin (Ruddock), but the drug had no effect in one of the writer's cases.

Of interest are the attempts at chemotherapy.

Mercuroehrome was given intravenously to 6 patients. Its effect seems to have been curative in 3, quite doubtful in 2, while in 1 it failed completely.

In Gage and Gregory's case the temperature became normal twenty-four hours after the first dose.

Belyea's patient was given 2 doses: the temperature became normal on the third day after the first dose, then rose again; it became normal on the day after the second dose.

Moore and Carpenter's patient received 2 injections, 30 and 35 cc. The patient was symptom-free after the first dose but the fever continued. The temperature "soon became normal" after the second injection.

One of the writer's patients remained symptom-free after the first injection (10 cc. of a 1-per cent solution) and for two days the fever was under 100° F.; then it rose again. After the second injec-

tion (15 cc.) the temperature again fell and for three days was under 100° F., only to rise again. A third dose (15 cc.) had no apparent effect on the temperature: four days later it suddenly fell to normal and remained so.

One of Warren, Smith and Linder's patients, who was given 20 cc., had fever for "six or eight days more."

A patient of Moore and Carpenter's continued to have fever four weeks after a 23-cc. injection of the drug.

One patient received 2 intravenous injections of acriflavine without effect. A single subsequent dose of mercurochrome was curative (Gage and Gregory).

Mercurochrome has been tried in Malta fever and, in South Africa, in abortus infection. Todd reports cures in 2 Malta fever cases in Texas. Ross and Martin in South Africa claim that the drug concentration obtainable in the blood has no action on brucella *in vitro*, and that its therapeutic action is consequently not likely to be efficient. They report 9 cases so treated: 1 was cured, 2 were "improved," 6 were not helped. Their dosage, however, seems to have been inadequate.

Vaccine therapy has been used in Malta fever but not in abortus infection. The reports of results have been more or less favorable. San Roman claims 84 per cent cures, and 86.5 per cent of these in less than twenty-five days.

Prophylaxis. From the standpoint of the individual this might seem fairly simple: the use of pasteurized milk, the avoidance of raw milk when possible, or the boiling, before consumption, of raw milk, including so-called certified milk. These measures will, of course, protect, but the likelihood of their universal adoption is most remote: the condition must be attacked at the source.

Here the problem assumes vast proportions. Abortus infection in cattle is present, and in high incidence, in every section of the country. Its effective control will require the most widespread and thorough campaign on the part of public health organizations and the continued intelligent coöperation of dairymen. One of the first steps must be to inform dairymen of the human health problem involved, both for themselves (raw milk, contact infection from diseased animals) and for the ultimate milk consumer. They are already well enough aware of the economic problem that bovine infectious abortion presents—a powerful incentive to carry out the proper precautions for protecting their herds.

Various methods of herd prophylaxis and treatment of infected animals have been proposed. Birch recommends the detection and segregation of all infected cattle. Such animals are to be recognized by the breeding history, the agglutination test of each individual in the herd over ten months old, including the bull, the examination of the genitals of all animals. The greatest care should be taken to prevent the introduction of infected animals into a herd. Karsten in Germany advises: (1) Blood agglutination tests in all

animals in the herd, including the bull, at least onee a year. Reacting animals are to be killed or segregated. (2) Newly-purchased cattle should be tested at onee, and if pregnant, should be segregated until after delivery. Before being put in the common stable they should again be tested. (3) Cows which abort or are prematurely delivered should be segregated until proven noninfeeted. (4) In freshly infected herds in whieh less than 10 per eent of the animals are involved, the disease is eradieable by killing the infected individuals, repeated disinfection of stables and routine testing of the remaining cattle. He feels that these more radical measures are preferable to the therapeutie vaecination when the incidenee of infection in a herd is low.

In Rhodesia infectious abortion in cattle has been made a notifiable disease. Infeeted herds are quarantined until six months after the last abortion or until satisfactory vaeeination has been carried out; stables are disinfected and reacting bulls are killed.

Vaccine treatment of segregated infeeted animals seems to meet with fair success.

Huddleson treated infeeted cows with intravenous injeetions of large doses of aeriflavine and of proflavine but without result.

Case Reports in Abstract. CASE I. A man, aged twenty-two years, was suddenly taken ill with fever, weakness and chilliness. Symptoms continued with anorexia, chills, sweats, eonstipation and loss of weight. The physieal examination was negative exeept for a slightly enlarged liver and some questionable rose spots. There was a slight seeondary anemia, slight leukopenia, negative blood and urine cultures, negative Widal, and a positive agglutination test for Brucella abortus in 1 to 5120 dilution. A continued fever with slight daily remissions lasted fifty-nine days, influeneed possibly by 3 doses of mercurochrome intravenously. The probable source of infection was raw milk from a known infeeted herd. There was no contaet with goats or eonsumption of goats' milk. There was a slight transient albuminuria and an unexplained phosphaturia with constantly alkaline urine.

CASE II. A school-boy, aged thirteen years, had slight (100° F.) daily unexplained fever for a few days, with no symptoms, negative physical findings and a normal leukocyte eount. Immediately after general anesthesia and tonsilleetomy there was a chill and a temperature rise to 105°. The following day the liver was palpable; there was a transient leukocytosis, followed by slight leukopenia; a negative Widal and a positive agglutination reaction for Brucella abortus in a dilution of 1 to 640. Blood culture was negative for Brucella abortus. The temperature beeame normal by lysis in eight days, remained so for twelve days, then rose again for two days to remain normal therafter. The agglutinin titer in the afebrile period was 1 to 320. The probable souree of infeetion was raw milk from a known infected herd on a boarding-school farm in Virginia. There was no history of goat contact.

Case Reports in Full. CASE I.—Harold P., aged twenty-two years, shipping clerk in a rose nursery, on November 7, 1927, felt cold and chilly after exposure to cold and dampness. For two days he remained at home because of weakness and what he thought was a cold. On November 10 he was found to have a fever of 103° F. and was put to bed. From the onset there were sweats and chills, usually at night; two of the chills were so severe that the bed shook and were followed by vomiting. The appetite was poor; the bowels costive, moved only by laxatives. The patient had no headache, backache or nosebleed, but occasionally complained of burning on urination. Typhoid fever being suspected, a Widal test was made on November 13 and was found to be negative. The man's past medical, family and social history was negative: He had always lived in West Grove, Pa., had never been out of the state and had worked at his present occupation for five years. On November 22 he was admitted to the Medical Division of the Hospital of the University of Pennsylvania.

Physical examination on admission was practically negative. It showed a well-nourished, rational, rather acutely ill patient with a dry coated tongue, a moderately full abdomen, three or four small lesions on the skin over the abdomen, not unlike rose spots. The liver edge was questionably palpable a finger's breadth below the costal margin; the spleen was not palpable. The heart and lungs, lymph nodes, thyroid and testes were normal. Rectal examination was negative. The temperature was 100° F.; pulse, 112; respirations, 28; blood pressure, 110 systolic and 70 diastolic. These negative findings, together with a leukocyte count of 5500, led to a tentative diagnosis of typhoid fever.

The blood counts are given in the table; a slight secondary anemia and a moderate constant leukopenia with a low neutrophil percentage are the only abnormalities.

	R. B. C.	Hb. per cent.	W. B. C.	Neut.	Lymph.	Mono.	Eosin.
Nov. 22, 1927	....	..	5,500	—	—	—	—
Nov. 23, 1927	4,440,000	85	6,100	64	33	2	—
Dec. 1, 1927	....	..	6,400	47	44	9	—
Dec. 10, 1927	....	..	5,100	—	—	—	—
Dec. 16, 1927	4,910,000	75	5,200	61	36	2	1
Jan. 10, 1928	4,870,000	90	7,300	—	—	—	—

The urine showed at times traces of albumin and during the whole of the patient's stay in the hospital was alkaline in reaction and contained a heavy precipitate of amorphous and crystalline phosphates. The alkalinity persisted in spite of continued full dosage with ammonium chlorid (up to 9 gm. daily). No cause for this condition was discovered.

Widal tests on November 23 and 30 were completely negative for Bacillus typhosus and the paratyphoid organisms. Blood cultures (November 23 and 30), a urine culture (November 27) and a feces culture (November 28) also showed no typhoid organisms. The diagnosis of typhoid fever was therefore abandoned.

The patient continued to have fever of a fairly sustained type, ranging between 100° and 103° F.; pulse and respirations were elevated in proportion. Chills and sweats, usually nocturnal, occurred almost daily. After the more drenching sweats the temperature reached normal for one observation on each of three days during the first twenty-seven days of illness, but there was not an undulant fever curve. Anorexia and weakness were the only additional complaints. Because of the chills and sweats, tuberculosis was suspected, but two Roentgen ray examinations of the lungs (November 27 and December 3) were negative. Roentgen ray studies of the sinuses and the urinary tract showed nothing abnormal. Malaria was suspected, and, in spite of four negative blood-smear examinations (November 27, 28, 30 and December 2) quinin was given for five days without effect.

On December 8 agglutination tests with the patient's serum and a culture of Brucella melitensis var. abortus (obtained from the Laboratory of Hygiene, Pennsylvania State Department of Health) showed complete agglutination in a dilution of 1 to 1280, and when repeated in the Hygiene Laboratory a few days later, in a dilution of 1 to 5120. Control tests with a number of other sera were negative. No absorption tests with other types of brucella were made. Further cultures were made of blood (December 14, massive culture on December 19) and urine (December 20, 29), but these continued sterile.

Other clinical examinations included a negative blood Wassermann (November 26), a blood urea nitrogen of 14 mg. per 100 cc. (December 6), a two-hour phenolsulphonephthalein elimination of 35 per cent and a plasma CO_2 of 67 volumes per cent (December 12).

On December 20, the forty-fourth day of his illness, the patient was given intravenously 10 cc. of a 1-per cent solution of mercurochrome. This was followed by a sharp reaction with chill, abdominal cramps and temperature rise to 102° F. For the next two days the temperature was normal, except for one rise each day to 100° F. On December 23, 15 cc. of 1-per cent mercurochrome were given, with another but less severe reaction and fever of 101.8° F. For three days the temperature remained under 100° F., then began to rise higher each evening, with normal morning temperatures. A third dose of 15 cc. of mercurochrome on December 31 had no apparent effect. Four days later, on January 4, the fifty-ninth day of illness, the temperature fell to normal and remained so until his discharge on January 15, 1928. After the first injection of mercurochrome all subjective symptoms disappeared and the patient felt quite well, in spite of continuing fever. In the course of his illness he lost 25 pounds in weight.

On January 10, after a week of normal temperature, the agglutination titer of the patient's serum for Brucella melitensis var. abortus was 1 to 640.

When last heard from (June 1, 1928) he was in normal health and had suffered no relapses in the intervening time.

Careful inquiry was made into the possible source of infection. The patient had not been away from home for many months prior to his illness. He never came in direct contact with cows or goats. He never consumed milk or cheese of caprine origin; in fact, he knew of no goats in his neighborhood. He drank raw milk from a small local dairy and it was established that infective abortion was prevalent in the herd from which the milk supply was obtained. No cultures of this milk were made.

Case II.—Robert D., a school boy, aged thirteen years, was admitted on July 5, 1928, to the Hospital of the University of Pennsylvania to the service of Dr. George Fetterolf for a tonsillectomy. During the first two days in the hospital, July 5 and 6, the temperature rose once each afternoon to 100.5°. On July 7 the writer was asked to examine the boy for a cause of the fever and for possible contraindications to tonsillectomy on that date. There was a history of a slight degree of fever for several days, his temperature having been taken, not because of any complaint on his part, but because his mother thought he did not look quite well. There was also a story of a skin rash ten and fourteen days before, attributed to contact with jelly fish while bathing. His previous health had always been good, except for an attack of scarlet fever and frequent sore throats.

Physical examination was negative throughout, except for chronically diseased tonsils. The blood count showed a slight anemia (4,100,000 red cells, 72 per cent of hemoglobin) and a normal white cell count (7500). The urine was normal.

The opinion was expressed that no contraindication to the tonsillectomy existed. The operation was accordingly done that afternoon under general anesthesia.

Four hours later the patient had a severe chill, lasting five minutes, followed by a rise of temperature to 105° F., some headache and later a profuse sweat. A second physical examination that evening was again negative. The leukocytes had risen to 17,000.

On the following day the temperature had fallen to 101° F., and the leukocytes were 14,000. A history was obtained at this time that the patient had been drinking raw milk while at boarding school in Virginia until the beginning of the summer holiday a little over three weeks before, and that since that time he had been using raw milk from two Pennsylvania dairies.

Agglutination tests were, therefore, requested for Brucella abortus and the typhoid group. The abortus test was positive in 1 to 640 dilution; the Widal was negative.

The patient's fever pursued a remittent course, falling lower each day and in eight days was normal. Three days after the chill the liver was palpable and remained so for three or four days, 1 or 2 cm. below the rib margin. It was not tender. The spleen was not palpable. The leukocyte count three days after the chill had fallen to 5600, with 35 per cent neutrophils, 62 per cent lymphocytes and 3 per cent monocytes. The urine on one occasion showed a trace of albumin and occasional casts. A chest roentgenogram showed nothing abnormal. Except on the day of the chill there were no symptoms at all. A blood culture taken three days after the chill was negative ten days later for Brucella abortus. No absorption tests were done.

The patient left the hospital after a week of normal temperature. At that time the blood count was much the same as on admission: 4,200,000 red cells, 74 per cent of hemoglobin; 8000 leukocytes, with 43 per cent neutrophils, 48 per cent lymphocytes, 6 per cent monocytes and 3 per cent eosinophils. The abortus agglutination titer was 1 to 320. The urine was normal. The patient had lost 9 pounds during his stay in the hospital.

Five days later there was a recurrence of fever up to 102.5° F. for not quite two days, without any apparent cause or attendant symptoms. The temperature then became normal and has remained so.

An attempt was made to trace the source of infection and with this result: From the boarding school it was learned that just before the close of school one of the cows of their herd of 25 had an abortion, and since the close of school 2 more have aborted. There is no history of contact with goats or rabbits.

Summary and Conclusions. 1. Brucella melitensis var. abortus infection is widely prevalent in cattle throughout the country.

2. The organism is pathogenic for man.

3. An increasing number of case reports from all parts of the country points to the growing importance of this disease as a public health problem.

4. Especially in rural communities and small towns is the problem acute because of the two-fold danger of infection: direct contact with infected animals, and the commoner utilization of raw milk.

5. There is as yet a very low index of clinical suspicion of the presence of the disease on the part of general practitioners, and as a result many cases are in all likelihood going undiagnosed.

6. Clinical consciousness of the disease will lead to the routine testing for brucella agglutinins in all undiagnosed fevers.

7. With the view to further such a clinical consciousness the clini-

cal data of available American case reports have been compiled, together with the more important laboratory procedures.

8. Two additional cases of what may reasonably be called Brucella abortus infection are reported, the first to be recorded from Pennsylvania, and one of them the first on record as arising in that state.*

* The writer is indebted to Dr. George Fetterolf for his kind permission to report Case II.

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REVIEWS.

NURSES, PATIENTS AND POCKETBOOKS. By MAY AYRES BURGESS, Director, Committee on the Grading of Nursing Schools. Pp. 618; 61 illustrations. New York: Committee on the Grading of Nursing Schools, 1928. Price, $2.00.

THIS long awaited report fully justifies itself. No one having to do with any phase of illness, either as patient, physician, nurse or hospital administrator, can fail to appreciate that the nursing problem is annually becoming more pressing for solution. When the Committee on the Grading of Nursing Schools, backed by the most important medical and nursing organizations of the country, undertook the survey of the situation, it was realized that at last the problem was being approached in a proper manner. This book represents the report on the first stage of the five-year program of the committee. The book has 618 pages filled with valuable data. Nine of the chapters present the facts and the figures; seven chapters consist of quotations taken *verbatim* from reports and questionnaires returned to the committee; eleven chapters discuss the implications of the study. It is in these last eleven chapters that the reader will find the most interest. No one can venture, in the future, to express an opinion concerning matters pertaining to nursing, who has not carefully read and digested this book. No one will be justified in judging the many questions which arise between nurse and doctor, nurse and patient, or nurse and hospital without reference to these data. Many of the results of this study will be unexpected by most readers; but however at variance with one's individual preconceptions the overwhelming statistics of this book will force an agreement with the conclusions presented.

It is impossible to give an adequate idea of the thoroughness of this investigation or of its broad-minded impartiality. A few excerpts follow:

Nursing schools are increasing rapidly in numbers; in 1900, for every 1000 physicians there were 90 nurses; in 1920, there were 1029.

In many districts there is no shortage of nurses, even unemployment. The difficulty is rather, for unpopular service, to get the kind of nurse he (the physician) wants, "Nearly three-fourths of all the physicians in all specialties report that it is harder for their patients to pay for a nurse than to get a good one."

It is above all a book to be studied and it cannot help but to give one furiously to think.

O. H. P. P.

GYNECOLOGY FOR NURSES. By HARRY STURGEON CROSSEN, M.D., F.A.C.S., Professor of Clinical Gynecology in Washington University Medical School, and Gynecologist to the Barnes Hospital and St. Luke's Hospitals. PP. 276; 365 illustrations, including one color plate. St. Louis: The C. V. Mosby Company, 1927. Price, $2.75.

THIS excellent manual for nurses is a fitting complement to Dr. Crossen's justly popular books for the gynecologist. He has divided the text in two parts, the first gives a comprehensive survey of gynecological diseases and treatment, and is quite sufficiently developed. The second part is a manual of gynecological nursing technique with quite exact details regarding preparations of various sorts, operations and minor procedures. The illustrations are numerous, the photographs and diagrams add a graphic emphasis to the text. This is a very worth while book for nurses and for those who have in charge the teaching of nurses. P. W.

THE THEORY OF EMULSIONS AND THEIR TECHNICAL TREATMENT. By WILLIAM CLAYTON. Second edition. Pp. 283; 42 illustrations. Philadelphia: P. Blakiston's Son & Co., 1928. Price, $4.50.

APART from its practical applications in the field of pharmacy the subject of emulsions is one of considerable theoretical importance to workers in physiology, pathology and the other so-called medical sciences. To such workers this book may be recommended as an excellent presentation not only of the fundamental theoretical aspects of the subject but of many of its practical applications as well. The fact that the present second edition is almost twice the size of the first one published in 1923 is an indication of the amount of new material which it contains. The valuable bibliography at the end of the volume in this edition has also undergone a corresponding expansion and has been made more serviceable by the classification of the titles under sixteen separate headings.

M. J.

THE SIMPLE GOITERS. By ROBERT MCCARRISON, C.I.E., M.D., D.Sc., LL.D., F.R.C.P., Lieut.-Col. Indian Medical Service; Pasteur Institute, Coonoor, S. India. Pp. 106; 143 illustrations. New York: William Wood & Co., 1928. Price, $4.00.

THIS small volume contains, in slightly amplified form, the author's report to the International Conference on Goiter held at Berne in August, 1927. Half of the book is occupied by illustrations.

the majority photomicrographs of various types of goiter, which are in general rather poorly reproduced. It presents his views on the classification, etiology, treatment and experimental production of the simple goiters, based on many years of observation. The principal forms of simple goiter are classified as chronic hypertrophic (parenchymatous), diffuse colloid and lymphadenoid. All of the author's opinions as to the etiology of simple goiter do not find unanimous acceptance. However, his emphasis on the fact that iodin deficiency is only one factor (and often an inconstant one) in its production, and that such agents as composition of the food, gastrointestinal infection, and systemic intoxication may be important, is worthy of more consideration than is given at present in this country. The book is well worth reading by all those interested in the subject. E. R.

STAMMERING: A PSYCHOANALYTIC INTERPRETATION. By ISADOR H. CORIAT, M.D. Pp. 68. New York and Washington: Nervous and Mental Disease Publishing Company, 1928.

THE psychogenetic approach is here unhesitatingly adopted and it is suggested that stammering be classed as an "oral neurosis," thereby discarding the theories of transitory auditory amnesia, spastic neurosis of speech, localized motor obsessional neurosis or a form of hereditary tic.

In the matter of treatment: "Stammering is not a speech defect but a psychoneurosis" . . . "consequently, special speech gymnastics are practically useless." The author employs, and has full confidence, in the psychoanalytic method. No case reports are given. N. Y.

STUDIES IN THE PSYCHOLOGY OF SEX: EONISM AND OTHER SUPPLEMENTARY STUDIES. Volume VII. By HAVELOCK ELLIS, Pp. 539. Philadelphia: F. A. Davis Company, 1928. Price, $5.00.

THE declining years of this shy philosopher and scientist bid fair to be accorded generous recognition, but it is recalled that about 1899, his publication dealing with the darker side of sex-life was, in the interest of public morals, ordered by the English authorities to be seized and destroyed. Haveloek Ellis is our greatest authority on abnormal sex psychology and has recently been the subject of an important biographical study.

The first section here concerns Eonism, named for the Chevalier d'Eon, an accomplished diplomat and likewise a historic personage. For a long time the Chevalier adopted feminine attire, was commonly

regarded as a woman, appears never to have had sex contact either with women or men, and whose body at autopsy was found to be that of an essentially normal physical man.

Other subjects treated are: The Doctrine of Erogenic Zones. The History of Florrie and the Mechanism of Sexual Deviation. The Menstrual Curve of Sexual Impulse. The Synthesis of Dreams: Study of a Series of One Hundred Dreams. The Conception of Narcissism. Undinism. Kelptolagnia. The History of Marriage.

Some of Ellis's work parallels that of Freud and a comparison is not to his disadvantage. The volume is written in faultless English.

N. Y.

MANUAL OF MEDICINE. By A. S. WOODWARK, C.M.G., C.B.E., M.D., F.R.C.P., Lecturer on Medicine and Dean of the Medical School, Westminster Hospital; Senior Physician to the Royal Waterloo Hospital for Children and Women; Medical Tutor and Senior Medical Registrar to King's College Hospital; Senior Resident Medical Officer, Royal Free Hospital. Third edition. Pp. 523. Edinburgh: Oxford University Press, 1927.

A THIRD edition of this excellent manual contains many additions to the previous text. Laboratory tests are discussed and interpreted in clinical terms, and not a little attention is given to treatment. Outline forms, which are at once inclusive and clear, are frequently used. These and a good index add to the ready usefulness of the book. The work is comprehensive in scope, and though omitting any section on diseases of the skin and appendages, includes those on mental and nervous diseases.

K. A.

SPECIAL DENTAL PATHOLOGY. By JULIO ENDLEMAN, Professor of Dental Pathology in the University of Southern California. Pp. 444; 371 illustrations, of which 318 are original and 4 are colored plates. St. Louis, C. V. Mosby & Co., 1927. Price, $7.00.

THE author clearly perceives that teeth, though separate and strongly individualized entities are not independent of the body to which they belong or the tissues by which they are surrounded, and treats them as living organs subject to changes that may be referred to both external and internal conditions.

He rightly assumes that neither the teeth themselves nor their morbid states can be properly understood without knowing a great deal about the saliva in which they are bathed, and which is subject to both physiological and pathological changes, and which acts as a culture medium of various microörganisms, some of which may

invade and injure both enamel and dentin, or without appreciating that there are variations in the quality of the blood that circulates through their pulps and diffuses through their substance, bringing with it opportunities for chemical change as well as for infections. Nor does he forget that the teeth are imbedded in the bones which they may injure, or by which they may be injured. All of these things are given their proper place and proportion of space.

The general plan and scope of the book is conventional, but it loses nothing, and perhaps makes a stronger appeal on that account, as it can more readily be referred to and consulted by both students and scholars, when too much time need not be spent in looking for what is wanted. J. McF.

MENTAL HANDICAPS IN GOLF. By T. B. HYSLOP, M.D., F.R.S.E., Member of the Medical Golfing Society, late Senior Physician to Bethlem Royal Hospital. Pp. 112. Baltimore: Williams & Wilkins Company, 1927. Price, $1.50.

"To the psychologist there is no more interesting question of study than that of a golfer about to putt." "Tranquillity with equanimity should be the ideal mental stance." Only by the application of such principles can a golfer hope to achieve par, a word whose first letter stands for practice, its second for automatism, its third for reason. This little book with its humorous presentation actually contains much sound wisdom. O. P.

AFFECTIONS OF THE STOMACH. By BURRILL B. CROHN, M.D., Associate Attending Physician to the Mt. Sinai Hospital, New York City; Member of the American Gastroenterologic Association; Member of the New York Academy of Medicine, Society for Experimental Biology and Medicine; Associate Member of Harvey Society; Consulting Physician, United States Veterans' Bureau. Pp. 902; 361 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, $10.00.

THIS textbook constitutes a valuable addition to the literature on gastroenterology. While a somewhat large volume for the presentation of the diseases of a single organ, it is not unnecessarily wordy, is easily read, nicely arranged for reference, well indexed and satisfactorily illustrated. Being entirely new, it avoids the fault, so common in revised works, of discussing clinical conditions in terms of discarded physiology and of devoting space to clinical tests that are no longer made use of. The chapters are short, and to each is appended an adequate bibliography affording ready refer-

ence to the original literature. The discussion of the functional disturbances of the stomach is particularly interesting and a distinction is drawn between abnormalities of secretion and motility without organic basis and the gastric neuroses. The chapters on the latter, written in collaboration with Dr. Abraham Kardiner, are from the purely psychoneurotic viewpoint and have a Freudian flavor. A few grammatical errors have crept in, as might be expected in a new book, and the reviewer would call attention to the legend under Fig. 41, in which "Max Einhorn" and "Rehfuss" should be transposed. T. M.

THE HUMAN BODY IN PICTURES. By JACOB SARNOFF, M.D., Associate Surgeon, United Israel-Zion Hospital; Attending Surgeon, Harbor Hospital; Consulting Surgeon, Infants' Home; formerly Associate and Instructor of Anatomy, Long Island Medical College, Brooklyn, N. Y. Pp. 120; 190 illustrations. Brooklyn: Physicians and Surgeons Book Company, 1927. Price, $2.00.

THIS manual, "to be used in collaboration with a series of motion picture films or film slides, is intended to serve as an explanatory and teaching guide for student and teacher." The book by itself can serve no purpose that is not better served by any good illustrated text on physiology or anatomy, and can make no possible appeal to practitioner or medical student. But in conjunction with motion pictures or slide films it might prove useful for elementary and nurses' training schools. K. A.

NUTRITION AND DIET IN HEALTH AND DISEASE.—By JAMES S. MCLESTER, M.D., Professor of Medicine at the University of Alabama, Birmingham, Ala. Pp. 783. Philadelphia: W. B. Saunders Company, 1927.

UNQUESTIONABLY the best book on this subject published. Valuable not only as an indispensable textbook for the student but as a reliable reference book for the practitioner. Perhaps there is no subject so poorly represented among the books owned by students and practitioners. Now that this work has appeared, the omission of it becomes inexcusable. To read it is to realize how much is known concerning nutrition and diet and how little one knows one's self. It is, in addition, a valuable review of biochemistry and physiology and one cannot fail to be impressed with the sound basis in these two fields upon which modern dietetics rests.

O. H. P. P.

PULMONARY TUBERCULOSIS: ITS ETIOLOGY AND TREATMENT. By DAVID C. MUTHU, M.D., M.R.C.S., L.R.C.P., Associate of King's College, London. Second edition. Pp. 403; 28 illustrations. New York: William Wood & Co., 1927.

THIS volume is written in a style quite different from most books dealing with the subject. The author emphasizes the importance of social and economic conditions in the etiology of the disease. Unless one is especially interested in the disease one would find the account too lengthy and suffering from repetition. In the chapters on diagnosis, one notices the absence of data concerning differential diagnosis as well as a paucity of opinion in regards to Roentgen ray. Under treatment too much emphasis is placed upon inhalation therapy, but it is to be noted that the author lays great stress upon fresh air, rest, feeding and time. Thoracoplasty is but briefly mentioned and pneumothorax treatment is considered still experimental. Under prevention, social and economic conditions are emphasized but care of sputum is omitted. I. K.

THE MENINGIOMAS. By HARVEY CUSHING, C.B., D.S.M., A.M., M.D., LL.D., Professor of Surgery in Harvard University. Pp. 53; 28 illustrations. Glasgow: Jackson, Wylie & Co., 1927. Price, 2/6.

THE first MacEwen Memorial Lecture is appropriately opened with fourteen pages of historical allusions to Glasgow surgery from Peter Lowe to McEwen, with the Hunters "never very far away." The olfactory meningiomas are treated in a surgicopathologic manner that reminds one of the larger work on the pituitary, though the absence of all histologic discussion is to be regretted. The advantages of bloodless electrosurgery are stressed. E. K.

BOOKS RECEIVED.

New Books.

Clinical Medicine. By OSCAR W. BETHEA. Pp. 700. Philadelphia: W. B. Saunders Company, 1928. Price, $7.50.*

Principles Scientifiques de Récupération Fonctionelle des Paralytiques. By GABRIEL BIDOW. Pp. 141; 45 illustrations. Paris: Le Livre Pour Tous, 1928. Price, 20 fr. A compact statement of principles and approved instrumental methods of rehabilitating the partially paralyzed.

Laboratory Manual of Physiological Chemistry. By MEYER BODANSKY and MARION S. FAY. Pp. 234; 9 illustrations. New York: John Wiley & Sons, Inc., 1928. Price, $2.00.*

* Reviews of titles followed by an asterisk will appear in a later number.

Nurses, Patients and Pocketbooks. By MAY AYRES BURGESS. Pp. 618; 61 illustrations. New York: Committee on the Grading of Nursing Schools, 1928. Price, $2.00.*

Prescribing Occupational Therapy. By WILLIAM RUSH DUNTON, JR. Pp. 144. Springfield, Illinois: Charles C. Thomas, 1928. Price: Cloth, $2.10, Paper, $1.35.*

The Duodenum. By PIERRE DUVAL, JEAN ROUS and HENRI BÉCLÈRE. Translated by E. P. Quain, M.D. Pp. 212; 127 illustrations. St. Louis: C. V. Mosby Company, 1928. Price, $5.00.*

Systemic Infections. By A. KNYVETT GORDON, M.B., B.C., B.A. (CANTAB.). Pp. 176. New York: William Wood & Co., 1928. Price, $4.00.*

Biological Chemistry and Physics of Sea Water. By H. H. HARVEY. Pp. 194; 65 illustrations. New York: Macmillan Company, 1928. Price, 10 s. 6 d.*

The Surgical Operations on President Cleveland in 1893. By WILLIAM W. KEEN, M.D. Pp. 251. Philadelphia: J. B. Lippincott Company, 1928.*

Addresses on Surgical Subjects. By SIR BERKELEY MOYNIHAN, BART. Pp. 348; illustrated. Philadelphia: W. B. Saunders Company, 1928. Price, $6.00.*

A Textbook of Actinotherapy. By D. D. ROSEWARNE, M.R.C.S. (ENG.), L.R.C.P. (LOND.). Pp. 237; 20 illustrations. St. Louis: C. V. Mosby Company, 1928. Price, $4.00. A reasonably successful attempt to present a popular subject in elementary form.

Surgical Clinics of North America. Chicago Number, Volume 8, No. 3, June, 1928. Pp. 219; 49 illustrations. Philadelphia: W. B. Saunders Company, 1928.

Chemotherapeutic Researches on Cancer. By A. T. TODD, M.D. (EDIN.), M.R.C.P. (LOND.). Pp. 127. London: J. W. Arrowsmith, Ltd., 1928. Price, 2 shillings six pence.*

René Théophile Hyacinthe Laennec. A Memoir. By GERALD B. WEBB, M.D. Pp. 146; 13 illustrations. New York: Paul B. Hoeber, Inc., 1928. Price, $2.00.*

New Editions.

Hay-fever and Asthma. By RAY M. BALYEAT, M.A., M.D., F.A.C.P. Second edition. Pp. 310; 76 illustrations. Philadelphia: F. A. Davis Company, 1928. Price, $3.50. A manual primarily for patients but with much valuable information for the practitioner as well. The new edition has been considerably enlarged, is well illustrated and costs little.

Gynecology. By WILLIAM P. GRAVES, M.D. Fourth edition. Pp. 1016; 562 illustrations, 128 in colors. Philadelphia: W. B. Saunders Company, 1928. Price, $10.50. This outstanding textbook on gynecology in consequence of an exhaustive review of the literature on the subject and the inclusion of resultant new material is most thoroughly up-to-date in this present fourth edition. Especially noted is the discussion of pelvic neoplasms.

Syphilis. By HENRY H. HAZEN, M.D. Second edition. Pp. 613; 165 illustrations. St. Louis: C. V. Mosby Company, 1928. Price, $10.00. This is the second edition of a very well known and useful American text which has established a place for itself in clinical practice.

The Physiology of Exercise. By JAMES HUFF MCCURDY, A.M., M.D., M.P.E. Second edition. Pp. 270; 15 illustrations. Philadelphia: Lea & Febiger, 1928. Price, $3.00.*

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Diagnosis of Pernicious Anemia by "Blood-haloes."—EVE (*Lancet*, 1928, 114, 1071) suggests a method of determining the size of the peculiar phenomenon of blood which can be secured by a method of diffraction grating. He suggests that this method is very much more simple without requiring a fairly expensive apparatus than the usual method of measuring the blood cells according to the method of Price-Jones. The only feature or this author's paper we can disagree with is that it does not take four hours' work with a costly projection apparatus to measure 500 cells. With a certain amount of experience the method can be done much more rapidly than he suggests.

Angina Pectoris: A Syndrome Caused by Anoxemia of the Myocardium.—In a very stimulating and suggestive article on angina pectoris KEEFER and RESNIK (*Arch. Int. Med.*, 1928, 41, 769) discuss and critically review the various theories as to the genesis of angina pectoris. They detail various ideas that have been advanced to explain the pain and the sudden death in angina. They bring forth evidence to show the relationship between angina and coronary obstruction and between this condition and other types of cardiac pain. Their thesis is to the effect that angina is caused entirely by lack of oxygen to the heart muscles. A disproportion exists between the demands on the heart and the oxygen supply to the heart, the oxygen supply being reduced below the requirements of the heart even when the individual suffering pain is at rest. They believe that this lack of oxygen explains every feature of angina pectoris. They definitely and dogmatically state that angina pectoris has but one cause: an anoxemia of the myocardium. In reading over this article, one is rather impressed by the fact that the authors are rather straining at a gnat in order to uphold

their ideas. It would rather seem to be a quibble as to whether the oxygen want of the muscles of the heart at a particular moment was due to this or that cause. It would seem that calling the condition anoxemia altered but slightly the idea of considering the condition an ischemia due to the lack of oxygen transported by the blood and that it was of no particular moment whether or not the blood supply was decreased. The physiologic fact remains that diminution of the blood to a functioning muscle causes pain in that muscle. The blood carried the oxygen and therefore it is rather difficult to see how the interpretation of heart pain has been advanced by speaking of the condition as purely an anoxemic one.

Acquisition of Specific Hypersensitiveness.—BALYEAT (*South. Med. J.*, 1928, 21, 554) writes that almost every aspect of the subject of human hypersensitiveness offers questions which up to the present time have been unanswered. One of the first that naturally presents itself concerns the factors that influence the acquisition of hypersensitiveness. In order to answer this question, the author has reviewed his large series of cases and has arrived at some rather definite conclusions. He feels that inheritance is the chief factor to determine the likelihood of a person's developing hay fever or asthma and that this individual will probably develop a sensitivity to a certain group or groups of protein substances. If this individual early becomes sensitive to one group, there is a very great tendency that he will become sensitive to another group of atopens, depending, of course, in part upon the frequency with which such a person is exposed to the atopen. He believes that this substance to which the patient becomes sensitive clinically is nonnitrogenous, probably enzymic in character and clinically, whether protein or nonprotein, the substance is found in cows' milk and breast milk.

The Influence of a Diet, High in Butter Fat, on Growth, Blood Formation and Blood Destruction.—When the original Minot-Murphy diet appeared, fat was excluded very largely from the diet with the belief that fatty acids are hemolytic in action and help to aggravate or to increase the hemolytic factor, whatever it might have been, that was presumably present in pernicious anemia. On the other hand, Koessler, recommending a diet high in vitamins, suggests that a very large proportion of that diet should be made up of fat derived from dairy products. This merely serves to illustrate the divergent ideas as to the use of fat, particularly butter fat, in the treatment of pernicious anemia or, as a matter of fact, in nearly any disease. At the suggestion of the late Dr. Francis Peabody, MÜLLER (*J. Clin. Invest.*, 1928, 5, 521) undertook feeding experiments with rats, giving them a diet in which 86.5 per cent of the caloric intake was in the form of butter fat. He found that on such a diet the young rats grew properly to adult size and adult rats held or added to their previous predietetic weight. There was absolutely no evidence of injury to the blood-forming organs. The slightly lowered hemoglobin content might be readily explained on the basis of a deficient intake of salts. The postmortem findings showed increased abdominal fat and fatty infiltration of the liver, but the bone marrow showed normal blood-forming constituents.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY, SCHOOL OF MEDICINE AND ASSOCIATE PROFESSOR OF SURGERY, GRADUATE SCHOOL OF MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Subcutaneous Injuries of the Abdominal Viscera.—VANCE (*Arch. Surg.*, 1928, 16, 631) claims that two types of lesions are produced by physical violence on the abdominal cavity and its organs. The first is represented by stab wounds and bullet wounds, which penetrate the skin and leave characteristic external marks. They are known as percutaneous injuries. The second type is due to the action of nonpenetrating blunt force which traumatizes the abdominal viscera, but which may or may not leave marks on the surface of the skin. The parenchymatous organs of the abdominal cavity comprise the liver, spleen, kidneys and pancreas. They are located in the epigastrium and are well protected from external violence, so that, as a rule, a marked degree of force is required to rupture them. The first complication that follows the accident is shock. Later on intraperitoneal hemorrhage results from the bloodvessels in the affected organs that have been torn by the rupture. In most instances death is the result of the hemorrhage. The other complications depend on the individual organ that has been injured. Ruptures of the liver occasionally give rise to an effusion of bile into the peritoneal cavity because of an injury to the biliary tract. Ruptures of the kidney cause trouble, because of urinary extravasations. Injuries to the pancreas occasionally cause cysts of a peculiar type. The injuries are of different grades and the surgical problem is not a simple one. In a few instances, especially in ruptures of kidneys, expectant treatment may suffice. Perhaps the safest procedure is to do an exploratory laporotomy and be guided by one's findings. The hollow abdominal viscera comprises the gastrointestinal tract plus its mesentery and the urinary bladder. They can be readily ruptured by a moderate force applied to the anterior abdominal wall, so that in many instances they may display few symptoms immediately after the injury. The usual complications which develop after the trauma are hemorrhage into the abdomen, usually from a torn mesentery or a peritonitis of a varying grade from the extravasation of urine or intestinal contents into the peritoneal sac. The only method of cure in these cases is by an early operation. Intestinal ruptures especially are more virulent than ruptures of the urinary bladder, because the contents of the former are more infective.

Remarks on Carcinoma of the Lung.—GRAHAM (*South. Med. J.*, 1928, 21, 199) reports that the increasing attention devoted in recent years to the subject of carcinoma of the lung has suggested to many that this form of cancer is becoming more frequent. Whether or not there is an actual increase in its frequency remains to be proven. It

is, however, sufficiently common to justify its removal from the realm of supposedly infrequent curiosities. Substantiation of this opinion can be found in the report of Seydel, who found at the Pathological Institute at Munich that nearly 2 per cent of all deaths were associated with a carcinoma of the lung. When a carcinoma occurs in the lung regardless of whether it is primary or secondary, it passes through the same sort of processes that a carcinoma does in other parts of the body, namely ulceration and infection. For this reason it is a frequent cause of pulmonary suppuration. The recognition of pulmonary carcinoma is important, not only to those who are interested in thoracic diseases, but to neurologic surgeons as well, because occasionally operations have been performed on brain tumors which were in reality only metastases from unrecognized carcinomas of the lung. In Fisburg's series of 36 cases of primary pulmonary carcinoma 11 per cent showed metastases to the brain or dura. For these reasons it is important to consider some of the principal features of pulmonary carcinoma. Metastasis from distant growths may, of course, occur in any part of the lung and they may be single or multiple. Primary lung carcinoma occurs in at least two and possibly three general groups: Those arising in the bronchial lining epithelium, those arising in the bronchial mucous glands and perhaps those arising in the alveolar epithelium. In the first type occur severe hemorrhages, pneumonitis, occlusion of bronchi with partial atelectasis. In carcinoma arising from the bronchial mucous membrane a frequent but not invariable finding has been that the tumor is confined to the wall of the bronchus and especially to the submucosa. When this limitation occurs there is usually a diffuse narrowing of the lumen of the bronchus, so that it becomes thick walled with a narrow lumen. In the third type of primary pulmonary carcinoma, namely, that supposed to arise from the alveolar epithelium, the tumor is diffuse, as a rule when it is first recognized.

Colonic Studies (High Cecum).—Kantor and Schechter (*Am. J. Roentgenol. and Rad. Ther.*, 1928, 19, 101) claim that the colon in the course of fetal development undergoes the progressive changes of migration, rotation and descent in which the cecum progresses downward from the liver crosses the crest of the ilium and comes to rest in the middle of the right iliac fossa. Although arrest of development may occur in any of the steps outlined, the discussion in this paper was limited to failures in consummating the stage of descent. It is the result of this failure that constitutes the high cecum, which occurred in 5.1 per cent of 1049 Roentgen rayed individuals. The high cecum is most frequently encountered in the male sex and in the sthenic habitus. The high cecum is not as frequently associated with certain reflex or toxic symptoms (headache, vomiting) as is the low cecum. Ileal stasis and colonic irritability seem to be closely associated phenomena. The relatively increased incidence of ileal stasis in high and normal as contrasted with low ceca may, therefore, be due to the greater irritability of the short colons. Constipation may be regarded as a function of colonic length. It appears to be least common in high ceca, most common in redundant colons. Appendectomy is performed most often in low, least often in high ceca. On the other hand, a pus condition of the appendix is found most commonly in high and least often in low ceca.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY.

The Therapeutic Value of Irradiated Ergosterin.—The curative value of irradiated ergosterin in rickets, as well as in other nutritional diseases, is becoming more definitely established. Thus Gyorgy has recorded the exceptionally rapid cure of 25 cases of rickets. Now STROTE (*Klin. Wchnschr.*, 1928, 7, 144) presents the detailed results of its use in three patients, treated under conditions of satisfactory control. The first was a case of extremely advanced rickets in a child, aged five and a half years, whose sister was also in a similar condition. Both were first treated with ultraviolet light, exposure of the body to fresh air and the administration of calcium, phosphorus and cod-liver oil, with but very slight benefit. The boy was then given irradiated ergosterin in doses of 1 to 3 mg. daily, other methods of treatment being withdrawn. Pronounced improvement was observed after scarcely three weeks of treatment, while the sister, who did not receive ergosterin, failed to improve and died in about six weeks. Within four months the boy was almost entirely well, both clinically and roentgenologically, and had gained 2.25 kg. of weight. The second patient was a woman, aged thirty-one years, suffering from advanced osteomalacia of several years' standing, who had been treated by various methods without material improvement. Beginning with 4 mg. per day, the dose of ergosterin was raised to 10 mg. Within four weeks there was obvious improvement in the patient's general condition, and continued administration brought about increased calcification of the bones, complete reunion of the multiple spontaneous fractures and pronounced gain in weight. The third was a child with marked tetany which had responded but slightly to the usual method of treatment. Marked improvement resulted from the administration of 2 mg. of ergosterin per day, amounting essentially to a cure of the patient's condition. In addition to these three cases the author reports almost universally satisfactory results in a considerable series of cases of rickets in various stages of its development. He recommends for infants a dose of 2 mg. per day, for children between one and three years of age 4 mg., and doses up to 10 mg. for adults if the best results are to be had.

The Dependence of Insulin Action on the Activity of the Female Sex Glands.—On the basis of animal experiments and of clinical studies VOGT (*Deutsch. med. Wchnschr.*, 1928, 54, 702) believes that there is a close relationship between the activity of insulin and that of the female sex glands especially related to the content of the sex hormone in the circulating blood. He points out that insulin is active in controlling the so-called ovarian bleeding, juvenile bleeding, the menorrhagia of the climacteric, and that resulting from uterine inflammations. In the use of insulin to improve the nutrition of nondiabetic patients he finds that

the action of this hormone is quite parallel with ovarian activity. Thus directly before menstruation, when the blood is richest in the menstrual hormone, the action of insulin is more pronounced, while it is feeblest in the first few days after menstruation. With the beginning of ovulation, that is from the middle of the intermenstrual period on, the action of insulin increases progressively. On the other hand, during pregnancy the action of insulin remains essentially stationary. Finally, insulin action can be markedly increased by admixture with blood serum taken directly before the time of menstruation or by mixture with a pure protein-free water soluble substance obtained from the ovarian follicles.

The Intravenous Use of Sodium Bicarbonate in Tetanus.—Working in a region in which tetanus is of frequent occurrence, HEIM (*Klin. Wchnschr.*, 1928, 7, 794) finds the antitoxic serum of little curative value, although he believes it to be of extreme value as a prophylactic. In an endeavor to improve the therapy in cases of developed tetanus he has employed intravenous infusions of from 40 to 70 cc. each of a 10 per cent solution of sodium bicarbonate in a small series of cases mostly in children in whom the prognosis is usually extremely unfavorable. He finds such injections bring about marked relaxation of the muscle spasms within fifteen to thirty minutes. The effect is sufficient to permit the patient to take food by mouth. The relaxation, however, lasts for only three to five hours and he, therefore, repeats the injection once daily and as soon as the patient can swallow he begins the oral administration of sodium bicarbonate endeavoring to give from 30 to 40 gm. per day. Under such treatment, the general condition of the patients is greatly improved, especially their nutrition. Six patients were treated by this method, five of whom recovered from their tetanus, the sixth, an extremely grave case, died on the fourth day of the disease, only one day after admission to the hospital.

Treatment of Arthritis Deformans with Parenteral Injections of Sulphur.—On the basis of the theory that the cartilaginous structures of joints possess a marked affinity for sulphur, and that this is probably disturbed in the presence of arthritis deformans, HABLER and WEITZENFELD (*Deutsch. med. Wchnschr.*, 1928, 54, 566) treated a series of 29 patients by the intramuscular injection of a suspension of sulphur in colloidal gelatin. The preparation employed was called Sufrogel. The authors began with initial doses of 0.1 cc. which were progressively increased at each succeeding injection, the effort being made to avoid both local and general reactions. The doses were spaced about eight days apart and usually required a series of 10 or more injections. Eleven of the patients remained entirely free from symptoms for periods of six to eighteen months. Twelve others whose arthritis was in a moderately severe stage at the beginning of treatment were sufficiently improved to be able to return to work without difficulty, although excessive activity of the joints still caused pain. In 2 patients there was no improvement, and in the remaining 4 only slight betterment was obtained. This last group were very advanced cases. The authors found the results so satisfactory that they did not employ other methods of treatment but they suggested the possible advantages of combining this treatment with nonspecific protein therapy.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

Abdominal Injuries in Children.—LEVIN (*Ann. Surg.*, 1928, 87, 718) studied 149 cases of abdominal injury in children and his results indicate that the commonest early symptoms in order of importance are abdominal pain, tenderness, rigidity, abdominal wall injury, moderate elevation of temperature, vomiting and leukocytosis. The mortality rate varies with such factors as the character of the injury, the extent and nature of visceral trauma, the time that elapsed between the injury and treatment, and the age of the child. The early effort to combat shock, blood transfusion and combined local and general anesthesia are very important considerations in successful treatment, in addition to the specific repair of the injured viscus. Laporotomy is justified whenever there is a reasonable doubt as to visceral trauma, and the general condition of the patient is good.

The Relation of Infantile Convulsions, Head-banging and Breath-holding to Fainting and Headaches in the Parents.—LEVY and PATRICK (*Arch. Neur. and Psychiat.*, 1928, 19, 865) state that the frequency of periodic headaches in groups of apparently normal women in five communities was 40.2 per cent. These headaches were largely migraine. Classified on the basis of time lost from work, the majority of periodic headaches caused slight incapacity. The frequency of fainting in apparently normal women was 28 per cent. It seemed that the parents who fainted or who suffered with periodic headaches were more likely to have children who had infantile convulsions, temper attacks with head-banging or breath-holding, and other recurrent attacks, especially spells of fainting or vomiting. Parents who fainted were more likely to have children of this type than parents who had periodic headaches but remained free from fainting. Parents who had frequent periodic headaches were more likely to have such children than parents whose attacks were infrequent. The same was true of fainting. On the other hand children who had the explosive symptoms were more likely to have parents who fainted and had periodic headaches, than children who were free from the syndrome.

Rheumatic Heart Disease.—MCCULLOCH (*J. Am. Med. Assn.*, 1928, 90, 2073) says that there are certain points that make it easier to determine when the child is convalescent and may be allowed increased activities. Each of these points are well known and were brought to attention by previous observers. Some of these points are more readily determined by those in constant attendance on the patient after a few simple instructions than by the physician. The following are the points for determination: Normal body temperature, a maximal

pulse rate of less than 100 per minute, normal pulse rate three minutes after exercise, progressive gain in body weight, absence of signs of fatigue, normal leukocyte count, normal erythrocyte count, normal systolic blood pressure, pulse pressure less than 50 mm., heart size stationary or decreasing, normal cardiac mechanism, absence of signs of cardiac failure, normal respiratory vital capacity, absence of skin eruption or hemorrhoids, absence of rheumatic nodules, quiescence in infections of nose, throat or other foci, and a period of normality for two weeks after the withdrawal of salicylates.

Essential Lipoid Histiocytosis.—ABT and BLOOM (*J. Am. Med. Assn.*, 1928, 90, 2076) found that the anatomic and clinical manifestations of essential lipoid histiocytosis were so characteristic that it should not be difficult to make the diagnosis on purely clinical grounds. If diabetic coma can be eliminated, a splenic puncture furnishes the evidence for an absolute diagnosis. In view of the fact that in a relatively brief experience with this disease, the authors were able to examine anatomically 4 cases and of following another case that was still under observation at the time of the report. They feel that the condition certainly cannot be as infrequent as the 15 cases now recorded would indicate. It is their hope that the attention of the profession be directed to this disease, so that more cases will be diagnosed and early enough to allow for some therapeutic procedure. The disease seems to be a disturbance of lipoid metabolism. While its exact nature is not clear, there are two possibilities, one of which is disturbed activity of the reticuloendothelial system in the intermediate metabolism of lipoids, and the other is a flooding of the entire body, for some as yet unknown reason, with lipoids, mainly lecithin.

Abscess of the Larynx in Infants.—MCINTOSH and NICHOL (*J. Am. Med. Assn.*, 1928, 90, 2095) report 5 cases of abscess of the larynx in infants, all of which recovered after surgical drainage. The principal symptom in 4 was dyspnea, and in 1 a swelling of the larynx without dyspnea. The severe degree of dyspnea, associated with aphonia and retraction, simulated the picture of laryngeal diphtheria, from which this condition must be differentiated. In 4 of the cases a laryngeal swelling was observed, which disappeared after drainage of the abscess. In 1 the abscess was discovered accidentally although a swelling had not been noticed. External drainage was effectual in all 5 cases. In the procedure of choice, the mass is first aspirated through the midline of the neck to confirm the diagnosis of abscess and to obtain material for culture. The skin is divided by a small transverse incision and the pus liberated by blunt dissection with a pointed hemostat. Relief of dyspnea and aphonia are immediately effected.

The Control of Fits and Betterment of Mental Symptoms in Epilepsy.—BROWNRIGG (*U. S. Vet. Bur. Med. Bull.*, 1928, 4, 413) advocates a plan for vigorous individual treatment of certain epileptic patients, with the object of not merely gaining slight improvement, but of definite cessation of fits, mental improvement and general rehabilitation. He does not suggest explanations of the mental mechanisms for the changes, and the procedures are based only on clinical experience with some success where others have failed. Phenobarbital properly and persist-

ently used caused cessation of epileptic attacks and improvement of mental status in a fair proportion of his patients. Finely divided in an emulsion, it is the preparation of choice and is superior to sodium phenobarbital. Improvement in young patients may amount to a praetical cure. With the resumption of physical and mental growth and vigor. Such treatment should be tried in all proper cases of epilepsy in which full coöperation can be secured.

The Relation between Mother and Fetus as Regards Blood Calcium —Bokelmann and Bock (*Arch. f. Gynec.*, 1928, **133**, 739) observed that the total amount of calcium as well as the absolute concentration of dialyzable calcium was higher in the blood from the umbilical cord than in the mother's blood. The relative value of the dialyzable portion on the other hand was somewhat higher in the serum of the mother. There appeared to be no parallel relationship between calcium content of the placenta and the stage of pregnancy or the need of calcium by the fetus. In the last months of pregnancy when the need of the fetus is unusually great there was a decrease in the calcium content of the placenta. Their results showed that the supplying of calcium is not a matter of a passive diffusion from the mother, but that active metabolic processes in the placenta are involved.

Report of 320 Fetal Postmortems at the Chicago Lying-in Hospital.—Serbin (*Am. J. Obst. and Gynec.*, 1928, **15**, 682) reviews a series of 320 fetal autopsies. There were 213 infant deaths and 107 still births, 60 of which were intranatal and 47 before labor set in so that there was maceration of the fetus. There were 45 cases of intracranial hemorrhage in operative deliveries and 18 in spontaneous deliveries. In 66 cases of asphyxia of the newborn with a diagnosis of atelectasis pneumonia, 48 babies were premature, 5 were full term spontaneous, and 13 were delivered by Cesarean section. One of these had an enlarged thymus. There were 13 monsters. Seven of these were associated with placental disease. Three had urogenital deformities and 2 had diaphragmatic hernia. There were 2 cases of sepsis of the newborn and 4 cases of pneumonia.

OBSTETRICS

UNDER THE CHARGE OF

NORRIS W. VAUX, M.D.,

CLINICAL PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA,

AND

CLIFFORD B. LULL, M.D.,

CLINICAL ASSISTANT IN THE OBSTETRICAL DEPARTMENT, JEFFERSON MEDICAL COLLEGE PHILADELPHIA.

Prophylactic External Cephalic Version in Breech Presentation.—A question much discussed in recent literature, that of external version receives attention again in "Prophylactic External Cephalic Version in

Breech Presentation." McGUINNESS (*Canadian Med. J.*, 1928, 19) by the standard textbooks of today give the fetal mortality in breech delivery as varying from 3 to 15 per cent. The New York Lying In Hospital report for 1924 showed a death rate of 16.4 per cent. While the Winnipeg General Hospital reports a fetal death rate of 19.8 per cent in 86 cases. If we accept the fetal mortality in vertex deliveries as 2 to 3 per cent, the advantage of substituting a cephalic for a pubic presentation is at once apparent. In the last three years the author has studied a total number of 62 breech cases with the following results: Version was tried in 59 cases and failed in 2. In 3 cases it was not tried, 1 a premature delivery and 2 cases of twins. The successful versions were done in 23 primiparæ and 34 multiparæ requiring one attempt in 48, two attempts in 6 and three attempts in 3. One case was done in the sixth month, 21 in the seventh month, 24 in the eighth month and 11 in the ninth month. The fetus was turned in flexion in 54 cases and in extension in 3 cases, care being taken to maintain flexion in all cases. All were delivered subsequently of the vertex save 1 which was delivered by Cesarean section. The only fetal mortality occurred in a case of maternal toxemia with premature separation of the placenta. Many objections have been raised against the performance of routine external cephalic version, as the occurrence of partial separation of the placenta, premature labor, danger of winding the cord around the neck of the fetus, the fetus may revert to its previous presentation, and possible prolapse of the cord in labor. The author encountered none of these difficulties. The cord was around the neck once in 12 cases, comparable to a normal vertex case and believes external cephalic version should be done in all uncomplicated cases of breech presentation.

The Toxicity of Blood Serum Proteins in Eclampsia.—LASH and WELKER (*Am. J. Obstet. and Gynec.*, 1928, 15, 511) assumes the blood serum in eclampsia to be more toxic than that in normal pregnancy but no effort has been made to separate the fractions of proteins and study the different fractions as reported in this article. The blood used was obtained from two eclamptic patients, (intrapartum and postpartum) and the fractionation carried out according to the method outlined by HEKTOEN and WELKER (*J. Infect. Dis.*, 1924, 34, 440). The blood serum proteins were disolved in normal saline solution and injected intraperitoneally into white mice. None of the blood serum proteins proved toxic in the experiments so the author concluded the blood serum proteins of normal and eclamptic women's blood showed no experimental evidence of toxicity in mice, although injected in large doses intraperitoneally.

Report of Five Years Activities of the Maternity Service, Secard Division of Bellevue Hospital.—This report by BAILEY (*Am. J. Obstet. and Gynec.*, 1928, 15, 462, 715) brings out some interesting facts. The predominant motive in this report is to show that an obstetric service in a General Hospital may be conducted with as little loss of life from childbirth as occurs in institutions devoted specifically to maternity work. The hospital protects the obstetric service by prohibiting vaginal examinations by ambulance surgeons and admitting officers and normal deliveries are conducted without rectal or vaginal examination. The

few vaginal examinatious neeessary in abnormal cases are made with antiseptic, as well as aseptic precautions. They believe also that rectal examination is quite as likely as the vaginal examination to carry infection to the upper part of the vaginal traet and therefore conduct normal labor with the abdominal examination alone. It is interesting to note that in spite of this, of the 8 patients who died of sepsis (of 4396 deliveries) 3 of these women were delivered spontaneously under their care without vaginal or rectal examinations during labor. Of the other 5 deaths from sepsis 1 was admitted after thirty-nine hours of labor and had only one rectal examination. The remaining 4 cases were delivered outside or attempts made to deliver before admission. The author believes that considerable success has been obtained from the use of polyvalent antistreptococcic serum and from intramuscular injections of boiled milk in cases of postpartum infection but do not have definite data to substantiate their belief. Patients with a temperature of 100.4° for two consecutive days, (excluding the first day) during the postpartum period are regarded as morbid. The morbid cases are divided into two groups, those with temperature due to uterine infection, and those due to medical or surgical cases. The fatal uterine or obstetric morbidity was 9.6 per eent higher than was expeeted in view of the fact that 58 per cent of the deliveries were eondueted without vaginal or rectal examinations. Comparisons of the temperature of patients who were examined vaginally or rectally with those who were not, show that in the former groups the rate was 6.6 per eent and in the latter 7.2 per cent. The slightly lower rate in the eases that were examined is explained by the fact that during the past year they had been using vaginal injections of 2 per eent mereurochrome as a routine procedure before examination as well as in all operative eases. The fetal death rate of 4.8 per cent, deducting the mascerated fetuses and abortions (including all stillbirths and neonatal deaths gives 9.2 per cent) is of interest when compared to the death rate of 15.4 per cent in breech deliveries. Operative procedures are reduced to a minimum with 93 Cesarean sections, 430 forceps deliveries, breech extractions totalling 227 cases and 77 cases of version and breech extraction. The author feels that their success is due to the limitation of vaginal and rectal examinations and the conservative use of operative procedure.

GYNECOLOGY

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Combined Method of Treating Cervical Cancer.—According to STEVENS (*Radiology*, 1928, 10, 57) the combination of Roentgen rays, radium and electrothermic coagulation offers some advantages over

the use of any one of these agents individually. In his clinic the treatment is begun with a thorough irradiation of the pelvic contents with the Roentgen rays which is repeated in two weeks' time. Upon completion of the second series of Roentgen treatments, the disease upon or within the cervix is destroyed and removed by means of electrothermic coagulation. This is a surgical operation and the term "electrothermic coagulation" at once conveys to one's mind that there is a production of heat by an electric current of sufficient intensity to coagulate the tissue to which it is applied. The operating electrode is cold at all times, the heat appearing only in the tissues treated and being caused by the oscillations of a high frequency current. As compared with excision it has the advantage of destroying the malignancy before it is removed, the growth being removed as a dead mass of tissue instead of as a mass of viable cells. This plus the fact that the lymphatics and bloodvessels are closed, tends to remove the possibility of mechanical metastasis. This treatment is painful and is done under a general anesthetic, generally gas and oxygen, never ether. As soon as the carcinoma is destroyed and removed, radium in the form of needles is buried deeply and evenly throughout the coagulated area and the cervical stump and a radium capsule of not less than 50 mg. is pushed through the cervix into the uterus, after which the vagina is tightly packed with gauze. From four to eight weeks later further Roentgen treatment is given, using rays of high voltage and this is followed by a five-year period of observation. With this method of treatment, according to the Schmitz classification, he has been able to obtain 100 per cent five-year cures in the Class 1, cases, 42.1 per cent in Class 2 and 11.3 per cent in Class 3, which of course is an unusually good showing.

Pregnancy following Irradiation of the Ovaries.—When we recommend irradiation of the pelvic organs in women in the child-bearing age the question is often asked: "Can I become pregnant after this treatment?" Of course pregnancy is extremely unlikely in any woman who has had a castration dose of Roentgen ray or radium but that it is not out of the question is demonstrated by the case reported by HOLTERMANN (*Zentr. f. Gyn.*, 1927, 51, 2091). This patient was a thirty-two-year-old tertipara with a rachitic flat pelvis who became temporarily sterile and amenorrheic following irradiation of the ovaries. Three years later she was delivered of a well-developed but dead child which showed no developmental defects. The death of the child occurred during labor and was probably due to the narrow pelvis of the mother together with the forceps used during deliver. Three months later she became pregnant again and went on to spontaneous delivery three weeks before term. The child was healthy and it developed normally during an observation period of two years. The mother continued to be amenorrheic. The case is interesting for two reasons, namely, that it demonstrates that conception is possible after Roentgen castration even though the patient remains amenorrheic and furthermore it shows that if conception occurs there is not likely to be any developmental defect in the child.

Delayed Operations in Salpingitis.—In presenting a statistical study based upon a series of 600 cases of salpingitis, RICCI (*New York State J.*

Med., 1928, 28, 9) makes a plea for delayed operative intervention. He states that chronic, nonpurulent, bacteria-free cases of salpingitis, subjected to an operation, show a minimal percentage of operative mortality and a minimal incidence of postoperative morbidity. Both the chronic purulent and the acute purulent cases of salpingitis operated upon either during the febrile attack or even as late as three weeks following an acute attack present a discouraging operative mortality rate and a distressing postoperative morbidity incidence. The postoperative morbidity is either an immediate shock, a violent postoperative febrile reaction, a persistent irregular septic temperature, or a prolonged discharge from an abdominally drained pelvis. Patients with sealed tubal or tuboövarian pus, whether sterile or otherwise, withstand the trauma of an operation poorly, and are much more prone to lapse into a state of shock. Absence of temperature, in his experience, is no indication of an absence of a more or less active pelvic infection. Smouldering tubal or tuboövarian foci are often afebrile and aleukoeytic and the trauma of a vigorous vaginal examination brings them to light, while the trauma of an operative procedure may prove disastrous. Not infrequently, patients with tubal or tuboövarian inflammatory disease are fever free, but present a persistent and marked leukocytosis. This factor categorically contraindicates operation. Gonorrhea of the Fallopian tubes is a self-limiting disease. Ricci believes that it produces but one attack of pain, fever and leukocytosis, namely, the initial one. When subsequent attacks occur, and adnexal masses are palpable, the gonococcus has yielded its endosalpingeal habitat to secondary bacterial invasions. Streptococci remain in adnexal masses and retain their virulence for a much longer period of time but they do diminish in virulence eventually, as evidenced by the recovery of several cases operated upon for streptococcic adnexitis. These recoveries occurred in patients with a long-standing history of the disease. He states that there is no known means of distinguishing the presence of streptococci from other organisms in adnexal masses previous to operation. All bacteria encapsulated within tubes or tuboövarian masses eventually, if surgically undisturbed for a sufficient period, tend to diminish in virulence, to become markedly attenuated and eventually to be destroyed. The encapsulated pus, once the bacteria are destroyed, gradually resolves into harmless fluids of lesser consistency. Patients with pelvic masses harboring organisms of various types, the streptococci included, may from an economic point of view, be considered below par but they are never totally incapacitated except during an acute exacerbation. As time goes on, the interval between attacks increases and the severity diminishes. The figures on which these statements are based are certainly very convincing. He has divided the series into three groups, each of which contains 200 cases. The first group represents the cases of acute salpingitis which were not operated upon and in which there was no mortality; the second group comprises the cases of chronic nonpurulent salpingitis that were operated upon and which shows a mortality of $\frac{1}{2}$ of 1 per cent; the third group embraces the cases of both chronic and acute *purulent* salpingitis which were subjected to operation and the mortality in this group was 14.5 per cent. It is hoped that those surgeons who still see no danger in operating upon "pus tubes" in the acute stage will read Ricci's paper very carefully.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
DEWAYNE G. RICHEY, B.S., M.D.,
MERCY HOSPITAL, PITTSBURGH, PA.

The Symptomatology, Diagnosis and Treatment of Laryngeal Tuberculosis.—In stressing the importance of prevention and early diagnosis of laryngeal tuberculosis, SPENCER (*Ann. Otol., Rhinol. and Laryngol.*, 1928, 37, 213) mentions hoarseness and tickling in the throat as early symptoms, and dyspnea, dysphagia and odynphagia as late manifestations of the disease. Such pathologic pictures as anemia, infiltration of the posterior laryngeal wall and the interarytenoid sulcus, ulceration, tuberculomata and edema are described. A table of differential diagnosis between laryngeal tuberculous, syphilis, carcinoma, actinomycosis, lupus, and chronic catarrhal laryngitis is given. Active treatment embraces rest for the larynx, solar laryngoscopy and cauterization when other methods fail.

Heliotherapy and Artificial Light Treatment of Tuberculous Conditions and Particularly Laryngeal Tuberculosis.—In a detailed account of the physicochemical and applied therapeutic properties of heliotherapy and artificial light, STRANDBERG (*J. Am. Med. Assn.*, 1928, 90, 1595) states that the sun, unquestionably, is the best of all sources of light in places where sunlight is available. Of the various artificial lights, he considers the carbon arc light as the one most nearly approaching sunlight, because it not only exhibits a continuous spectrum, rich in blue, violet, and especially long ultraviolet rays, but it is also highly efficient in both infra-red and luminous red rays. After a discussion of the best types of lamps, the procedures in light therapy—as employed at the Finsen Medical Light Institute—are given. Although local light treatment is recognized as an adjunct, the author is convinced that the universal light bath is the method which will yield the best results, with the least inconvenience to the patient, for some time to come. By means of the universal carbon light arc bath, he has been able to effect cures in 86.6 per cent of 435 patients with rhino-laryngologic lupus vulgaris. In 41 cases of aural tuberculosis in which operation and light treatment were instituted, only nine ears are not dry. Interesting are the statistics from a series of 203 cases of laryngeal tuberculosis. The larynx was cured in 113 of these cases (55.6 per cent). Seventy-seven of the 113 had intrinsic tuberculous lesions, 34 had both intrinsic and extrinsic disturbances, and only two had purely extrinsic involvement. All of the 203 patients had pulmonary tuberculosis also. Before treatment, 110 of the cured patients were hoarse. After treatment the voice became clear in 90 instances. Pain and difficulty in swallowing disappeared in each of the 35 individuals in whom these symptoms occurred.

The Pathology of Mastoiditis in Infants.—Previous references (retrospected in AM. J. MED. SCI., 1927, 174, 431 and 1928, 175, 711) have been made in these columns to a type of otitis media and mastoiditis, occurring in infants, which is not infrequently associated with such systemic manifestations as fever, diarrhea, vomiting, loss of weight and athrepsia, and in which recovery sometimes follows the performance of mastoidectomy. Although some of these cases are more or less obscure, due to the absence of such striking evidence of mastoid involvement as postaurieular swelling, redness, tenderness or fluctuation, those who have brought this condition to our attention have emphasized the fact that certain definite otologic findings—such as changes in color and sagging of the tympanic membrane are practically always found, and that a close coöperation between the pediatrician and the otologist is necessary for the successful interpretation and management of these cases, so that any tendency to subject these babies to unwarranted operative interference might be obviated. In seeking an adequate explanation of this phenomenon, McMAHON (*Arch. Otolaryngol.*, 1928, 7, 13) examined, microscopically and bacteriologically, materials removed at operation from 71 mastoids of 39 infants. The cases are divided into four classes and the data are tabulated for each class. Briefly, it was learned that those cases presenting the "diarrhea-vomiting symptom complex" clinically, and an edema of the mucosa of the mastoid antrum microscopically, offered a bad prognosis; whereas, a better outlook could be expected in those instances in which there occurred a fibrosis of the mastoid antral mucosa—even in the presence of the "diarrhea-vomiting complex." When this syndrome was absent, the prognosis was equally good whether the mucosa of the mastoid antrum showed edema or fibrosis. The author believes that the occurrence of a nonresistant, highly permeable mucosa in those cases showing edema, and of a resistant mucosa of low permeability in those exhibiting fibrosis, offers a plausible explanation of the reason for deaths and recoveries in these groups. Bacteriologic examinations revealed several different types of microörganisms, none of which, however, was associated with any particular type of pathologic change.

A New Aid in the Diagnosis of Mastoiditis.—In comparing the calcium content of pus from discharging ears which showed frank necrosis of the bone with that obtained from pus in which osseous necrosis could not be demonstrated, FRIESNER and ROSEN (*Arch. Otolaryngol.*, 1928, 7, 317) found a strikingly high-calcium content in those cases in which necrosis of bone was present. The method of determination of the calcium content is described. The authors hope to stimulate others along these lines in order to accumulate a voluminous amount of statistical material. They believe that, if on the basis of extensive analyses the high-calcium content in pus is closely parallel to the presence or absence of necrosis of the bone, this test may prove to be an absolute indication for operative intervention.

Differential Jugular Blood Cultures in Sinus Thrombosis.—Since his preliminary publication, retrospected in AM. J. MED. SCI. (1927, 174, 29), OTTENBERT (*J. Am. Med. Assn.*, 1928, 90, 1601) has employed his method of culturing the blood, aspirated simulta-

neously from the two internal jugular veins (and preferably also from an arm vein) in 11 additional cases, making a total of 15. From the results of these cultures, which he gives and discusses, the author states that the practical value of the procedure is beginning to be more clearly defined, and, that perhaps of more importance than its diagnostic use, is the new light which the method throws on the mechanism of blood-stream infection in sinus thrombosis. In cases of thrombosis of the lateral sinus, the blood from one jugular vein usually shows a far larger number of colonies than that from the other jugular vein or from the arm vein. In the more common instance in which the thrombus completely occludes the sinus, the larger number of bacteria are found not in the blood from the diseased side but in that from the normal side. In the less frequent instance of a mural, nonocclusive thrombus, the larger number of bacteria are found on the diseased side. The cases cited showed that the bacteria were killed in, or removed from, the circulating blood with great rapidity. The procedure is simple and safe.

RADIOLOGY

UNDER THE CHARGE OF

ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,

CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

Primary Carcinoma of the Lung: II. Bronchial Type.—In a preceding paper, an abstract of which was published in this section, KIRKLIN and PATERSON discussed the roentgenologic characteristics of parenchymal carcinoma of the lung; in their present paper (*Am. J. Roentgenol. and Rad. Therap.*, 1928, 19, 126) they consider the bronchial type, of which 28 cases were observed at the Mayo Clinic. Pathologic examination of the growths showed about equal numbers of epithelioma and adenocarcinoma, most of which were highly malignant. Clinically, the dominant early symptoms were unusually persistent cough and periodic hemoptysis or constantly blood-tinged sputum. Often pain and dyspnea did not appear until late in the disease. As in all cases of carcinoma of the lung, loss of weight is a striking symptom. The major roentgenologic characteristics are a shadow at the hilum and atelectasis or bronchiectasis. The hilar density is roughly triangular, apex out. It has no clear-cut edge, but throws out strandlike processes into the lung tissue along the bronchial tree. Atelectasis, the second characteristic, is not constant; it appears over the lobe tributary to the bronchus involved, and although it is not diagnostic of malignant disease, it is diagnostic of organic bronchostenosis for which a cause must be sought. Bronchiectasis, which sometimes occurs as a result of the bronchial obstruction, is evident as a mottled fan-shaped shadow in the area affected.

Colloidal Contrast Media in Roentgen Ray Diagnosis.—In the opinion of BLUHBAUM, FRIK and KALKBRENNER (*Fortschr. a. d. Geb. d. Roentgenol.*, 1928, 37, 18) the usefulness of a contrast medium in roentgenologic diagnosis is enhanced if, instead of filling the hollow viscera completely, their internal surface is coated with the substance so as to yield a relief picture. After experiments with various media, the writers selected thorium dioxydhydrosol, which had proved to be harmless to animals. The drug is used in dilute solutions and in small amounts. Coating of the viscera depends on the fact that the secretions usually consist of negatively charged particles which caused a positively charged contrast medium to be precipitated on the wall. The new medium has been used successfully for roentgenography of the bronchi, and is regarded as superior to lipiodol because the injurious effects of the iodin component in the latter are eliminated.

Infantile Scurvy.—Although concerned chiefly with the roentgenologic manifestations of scurvy, BROMER (*Am. J. Roentgenol. and Rad. Therap.*, 1928, 19, 112) reviews the entire subject very lucidly. The disease arises from a defective diet, lacking a necessary vitamin. The greater prevalence of the disease in English-speaking countries is supposed to be due to the greater use of proprietary foods in infant feeding. Of these foods, those containing condensed or desiccated milk in connection with farinaceous foods are most frequently the cause. Approximately 80 per cent of cases occur between the ages of six and ten months. Rickets, congenital syphilis and scurvy occur in this order of frequency. Clinically, there is marked tenderness and loss of movement in the limbs, more often noticeable in the lower extremities. With the tenderness there is associated swelling, and rarely hemorrhagic discoloration of the skin, not limited to the epiphyseal regions but extending upward along the shafts of the long bones. The swelling and loss of movement is often greater in cases showing epiphyseal separations on Roentgen ray examination. At times edema may be noted in the swollen areas. Bleeding from the gums may be present but more often only a purplish line of discoloration is seen at the free edge of the gums. The middle portion of the hard palate may sometimes show discoloration and hemorrhage, while orbital hemorrhage is comparatively infrequent. Either macroscopic or microscopic blood is often found in the urine. Bleeding from the mucous membranes is uncommon. A rise in temperature is not unusual. A very high temperature would suggest an associated pyelitis. The association of pyrexia with joint changes has led to an erroneous diagnosis of acute osteomyelitis. In the very early cases of subacute infantile scurvy, as described by Hess, the symptoms are insidious and inconclusive. The patient is usually in the second half year of life and does not gain in weight or gains very little for weeks. Even if well nourished he is pale and sallow with perhaps edema of the upper eyelids. He is peevish and irritable and the appetite is poor. The gums often show a slight lividity or peridental hemorrhage which on subsequent examination may no longer be visible. Often only a rim of crimson, edging the borders of the upper gum, behind an upper incisor can be seen (Still). The papillæ of the tongue may show congestion and a petechial spot may be present on its frenum or on the palpebral conjunctiva, or here and there on the surface of the

body where there are erosions, eczema or other skin lesions. The urine may be diminished in quantity but more often is normal and sometimes may contain a trace of albumin or a few red blood cells. The pulse is rapid and becomes markedly rapid and irregular on the slightest movement and excitement. The respirations are also increased in rate. The knee jerks are sometimes exaggerated. The author divides the roentgenographic change into four stages: The clinically early or latent type of case exhibits the changes of the first stage, the most consistent sign of which is the smooth transparent ground-glass appearance of the shaft, especially near the diaphyseal ends. A broadened dense zone of temporary calcification at the very end of the shaft is also present. The cortex exhibits pencil-point thinning. A sign described by Wimberger, a dense calcified edge or ring about the epiphyseal center of ossification, is very constant. That portion of the ring nearest the joint is usually broadened while that nearest the diaphysis is thinner. This is due to the fact that growth is more rapid on the side nearest the joint. At the center is the same ground-glass appearance as noted in the shaft. In the second stage a zone of decreased density appears just behind the dense broadened line of temporary calcification at the end of the diaphyseal shadow. This represents the histologic change, the framework marrow zone. In addition, the first signs of hemorrhage may appear, as evidenced by the formation of lateral spurs just at the diaphyseal end. The third stage is that of well-developed subperiosteal hemorrhages which usually exhibit the density of beginning calcification within them. In childhood the periosteum is loosely attached to the shaft, but at either end of the diaphysis it is firmly attached where it becomes continuous with the capsule of the joint. On the roentgenogram, accordingly, the hemorrhagic effusions end abruptly at the point of attachment. It is in this stage that epiphyseal separations most often occur. The fourth stage is the stage of absorption of hemorrhage and repair of the scorbutic lesions. Progressive decrease in the length and breadth of the hemorrhages can be seen if repeated examinations are made. Periosteal thickening may persist long after healing has begun. The zones of temporary calcification become broader and denser; the framework marrow zone gradually disappears and becomes more calcified than the remainder of the shaft; in time the ends of the shafts show double lines of calcification stretching across them. Roentgenologic differential diagnosis may require consideration of sarcoma, osteomyelitis, syphilis and rickets.

Colonic Malignancy.—From a review of fifty cases, McGUFFIN (*Radiology*, 1928, 10, 21) concludes that there is no more insidious form of malignant growths than those of the colon or rectum. The patient is usually beyond the age of forty-five or fifty years and has previously enjoyed good health. Men are affected more often than women, in the ratio of 3 to 2. Sections of the colon attacked are, in order of frequency, sigmoid, rectum, cecum, descending, transverse, ascending. The growth develops slowly but early symptoms are likely to be slight, and when the patient comes for examination the disease is well advanced. Roentgenologic diagnosis is correct in a high percentage of cases.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO, DENVER, COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO.

A Further Discussion of College Mental Hygiene.—MORRISON (*Ment. Hyg.*, 1928, 12, 48) claims that: "Besides offering instruction in the various branches of science, literature and the arts, it is the duty of a university to give its students sufficient information concerning their physical and mental welfare so that they may make the most of their opportunities. They should not be handicapped by unnecessary physical illness or mental stress." He sketches the rapid advance from 1922, at which time seven universities were planning moves in the direction of mental hygiene, to 1927, when "at a meeting of college mental hygienists . . . twenty-one psychiatrists were present, including three from preparatory schools." As to incidence of emotional difficulties "there are no definite statistics available," and the author reviews the studies that have so far been made on unselected groups. All of these show a relatively high incidence of emotional difficulties. As to the relation of personality disorders to physical disease, the studies so far made are confusing, but the author finds in his own studies a higher incidence of physical defects among the maladjusted. He reviews 50 cases studied during the college year 1926-1927. Seven of these were voluntary patients, 28 were referred from the student health service and the rest from other sources. All classes from freshmen to seniors were about equally represented. Physical difficulties were responsible for 8 cases. The psychogenic causes were often multiple. In general, he states, family difficulties "accounted directly for a third (of the cases) and probably indirectly for a great many more. Ignorance and anxiety associated with sex or love affairs were the immediate cause of one-fourth. Worry over finances, difficulty in adjusting themselves to the college environment, the confused thoughts of the adolescent and improper methods of study were other etiologic factors." Thirteen of these cases were adjusted in one interview, 23 required two or more consultations and 15 of these made excellent adjustments. There were 4 failures. "The results with the remainder were unsatisfactory, due in part to insufficient time for observation and in part to lack of proper personnel to follow up these cases and to attack etiological factors outside of the university." He offers no detailed plan for the organization of a mental hygiene program in the university, but calls attention to the following points which he considers important: (1) Personal touch with all the students should be made, but this is impossible with a limited number of psychiatrists in a large student body. (2) Hence, the personal interview may be in

part replaced by lectures to selected classes, informal talks to smaller groups, or through contacts with the faculty members. (3) This calls for stimulation of the interest of the faculty. (4) The work should be conducted in intimate association with the student health service. (5) There should be close coördination with all the university departments.

Schoolroom Hazards to the Mental Health of Children.—MYERS (*Ment. Hyg.*, 1928, 12, 18) states that the competition among educators for speed in class work is building up a number of hazards to the mental health of school children. The necessity for speed imposed upon school teachers by their superiors is reflected in the schoolroom as praise for the speedy and impatience for the slower students, without enough regard for the quality of the work. This works to the detriment of the slower students who most need careful training. This difficulty is increased by the tendency of the curriculum experts to crowd new activities into the already overcrowded time of the schoolchild. He notes with approval the recent development of self-teaching texts in which the student is allowed to proceed at his own pace and the tendency in some schools to reduce the number of specific facts the child is supposed to learn in a given time. He makes the following suggestions for educators: (1) First recognize that the most effective learning presupposes a comfortable learner. (2) Let the educational testers call a halt to their testing program. (3) Remove all speed suggestions from the schoolroom; substitute accuracy and calm for carelessness and haste. (4) Let supervisory schemes be simplified. (5) Let more be done to relieve the teacher of unnecessary work and encourage her to introduce more human touches into her teaching. (6) Let those responsible for the curriculum lessen the number of specific facts and skills which the average child is supposed to master in a given time. (7) Let educational experts and school officials confer more frequently with parents to discover how they feel about the curriculum and methods of the modern school. (8) To the school psychologist add the school neuropsychiatrist who will check up on the mental health of schoolchildren and teachers and advise the school authorities as to methods and curricula in terms of mental hygiene.

Spirochetosis of the Central Nervous System in General Paresis.—DIETERLE (*Am. J. Psychiat.*, 1928, 7, 547), in investigations upon routine material (formol-fixed brains from state hospitals), using Jahnel's methods, found 25 per cent positive for spirochetes in 12 brains examined. All positive cases corresponded to the disseminated type except 1, a case of juvenile paralysis that showed the organisms in discrete swarms. The negative cases were determined by routine examinations of a few sections taken from the principal regions, especially the frontal cortex. Jahnel's total block impregnation methods were tedious. In addition to the above positive [illegible] spirochetosis was found in a case of accidental strangulation. The spirochetes were found principally in the cortex of the frontal lobes, especially in the gyrus rectus. They were also found in the central and temporal regions and in the hippocampal gyrus and in the basal ganglia. The cortex showed no evidence of atrophy. The author mentions, in connection with Jahnel's technique, a method for the demonstration of the spiro-

chete in single mieroscopie seetions but does not deseribe it. He presents a case in whieh it was used. In this ease the spiroehetes were in dense swarms and visible to the naked eye as blaek patches in the stained sections. "Many of the eolonies measured a millimeter in diameter" and less dense aggregations spread even more densely. They were eommonly loeated in the perivaseular lymph spaee and kept a fairly accurate surfaee distanee, being in the middle of the gray substance. The long axis of the bodies were eommonly tangent to the are of the vessels in eross-seetion. "Many pass through the vaseular wall at right angles or otherwise, some half within or without, and in a few instances they are seen within the lumen lying among red eells. In capillaries their numbers are so vast that the separate vessel elements are indistinguishable." Subpial swarms were found in the Isle of Reil. They were also found in the basal ganglia and in the eerebellar eortex. "The white substance eontained no organisms in the numerous speeimens examined and in the two infiltrative foei of the adrenals and in the aorta we have been unable to show them in one trial." The author designates the perivaseular swarms as "perieapillary eolonies." Nissl stains confirmed this viewpoint. He explains the distribution in the middle cortieal region on the basis of the short vessels of the eortieal blood supply. The subpial eolonies, he thinks, would confirm the idea of lymphogenous dissemination and the spirochetes in the bloodvessels tend to prove Jahnel's idea of this as the mode of remoter dissemination. The perivaseular arrangement he would aeeount for on the basis of meehanieal faetors sueh as pressure and the supposed tendency of the organism to migrate toward the ehief sourees of nutritional supply. The author is inelined to believe that the ganglionie system of vessels is first involved and the eortieal system seeondarily. Absenee of spirochetes in the white substanee is aeeounted for by the eentrifugal flow of lymph. The avenue of entry to the nervous system had not been determined.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
OSKAR KLOTZ, M.D., C.M.,
PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,
AND
W. L. HOLMAN, M.D.,
ASSOCIATE PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Anaphylaxis and Tissue Culture.—It would appear from the work of MEYER and LOEWENTHAL (*Ztschr. Immunitatsforsch. u. Exp. Therap.*, 1928, 54, 420) that the tissues of guinea pigs sensitized to horse serum are not inhibited in their growth in tissue culture by the presenee in the culture of horse serum. They used splenie, lymph gland, subeutaneous connective and pia mater tissue. Tissues from normal animals could not be sensitized by growing them in the plasma of sensitized animals, and even when the tissues were taken from animals which

had died of anaphylactic shock, these tissues gave normal growth in tissue culture. Heart muscle tissue from embryo guinea pigs also could not be passively sensitized. The plasma of sensitized guinea pigs was definitely growth inhibitory as compared with normal plasma against the tissue culture of either normal or sensitized animals. Foreign serums varied in their inhibiting power according to the animal species. The conclusion was reached that the tissue elements studied probably do not take part in the anaphylactic reaction, or may be only slightly affected by it. The authors believed more attention should be given to other cell elements such as those of the autonomic nervous system in the further study of anaphylaxis.

Microbic Associated in Appendicitis—The Rôle of the Enterococcus.—This pleomorphic coccus frequently found in appendicitis and which on isolation prefers anaërobic conditions, grows abundantly in the presence of bile in peptone water, is nonhemolytic and is practically always nonpathogenic for animals, was used by WEINBERG and DAVESNE (*Compt. rend. Soc. de Biol.*, 1928, 98, 196) in an interesting study of bacterial association. They injected the enterococcus along with acrobic and anaërobic bacteria such as are often recovered from appendicitis cases and found that it definitely raised the pathogenic action of B. coli, B. proteus, Friedländer's bacillus, B. perfrigens (B. welchii), and Vibrion septique while other combiations were without effect. Antienterococcus serum has been prepared to supplement the other antisera already successfully used in the treatment of appendicitis.

Tubercle Bacilli in Latent Tuberculous Lesions in Lung Tissue without Tuberculous Lesions.—OPIE and ARONSON (*Arch. Path. and Lab. Med.*, 1927, 4, 1) report the results of a study of the lungs from 169 autopsies in which 304 lesions with characteristics indicating a tuberculous origin, were examined for living tubercle bacilli. The subjects in all instances died from causes other than tuberculosis and lesions were considered latent when they were unaccompanied by symptoms or physical signs recognized by the physician. In tuberculous lesions of children or those situated in any part of the lung and associated with corresponding lesions in adjacent lymph nodes, it was found that living tubercle bacilli were present in from 33.3 per cent of caseous lesions, which were partly fibrotic, to 4.4 per cent of caseous encapsulated nodules. In adult lesions or those having origin in the apex and unaccompanied by tuberculosis of lymph nodes, the percentages of living tubercle bacilli varied from 76.2 per cent in fibrocaseous tuberculosis of the apex to 24.4 per cent in fibrous scars of the apex, and none in fibrous scars of apical pleuræ. Because tuberculosis was successfully produced in animals in 8.2 per cent of the cases by injection with material from calcified nodules in cases where no apical lesions existed; whereas with similar material in cases with apical lesions, tuberculosis was produced in 24.2 to 30.2 per cent of cases, it was thought that bacilli were present in the surrounding lung tissue. Consequently glands and pulmonary tissue apparently free from tuberculous lesions were removed and animal inoculations performed in some 33 cases. It was found that living tubercle bacilli were present in more than one-third of the apices

examined, slightly less frequently at the base of the lung and in 25 per cent of tracheobronchial lymph glands. They conclude from this that the greater percentage of living tubercle bacilli obtained from calcified lesions are from surrounding lung tissue; and the apical lesions of adult life make their appearance at a time when the lesions caused by tuberculous infection of childhood no longer contain living tubercle bacilli; that is that they are the result of exogenous infection.

Streptococcus Sepsis and the Reticuloendothelial System.—The reticuloendothelial cells are considered by many investigators to be the site of the production of antibodies and the defence mechanism against infection. Experimental proof of this has been developed by interfering with the functional activity of these cells, such as the attempts to "block" the system by injecting various negatively charged colloids, removal of the spleen, as the greatest complex of reticuloendothelial cells and combinations of these proceedures. MEERSOHN (*Ztschr. Immunitätsforsch. und Exp. Therap.*, 1928, **54**, 313) following the earlier work with spirochetes of relapsing fever which had shown the protective function of these cells, used hemolytic streptococci in mice and demonstrated that the removal of the spleen increased the death rate of injected mice from 20 to 40 per cent. The presence of streptococci in the blood stream, either at the time of death, or when the animals were killed six weeks after the infection, was increased from 64 per cent in the controls to 74 per cent in the splenectomized, and to 80 per cent in those previously splenectomized and injected with 0.5 cc. of a 5 per cent solution of ferric saccharate. The "blocking" after splenectomy did not increase the mortality over that of mice in which the spleen alone was removed.

Mechanism of Allergy in Tuberculosis.—In attempting to learn whether the cells of an allergic animal are more sensitive to the effects of the products of the tubercle bacillus, RICH and LEWIS (*Proc. Soc. Exper. Biol. and Med.*, 1928, **25**, 596) used the method of tissue culture. Their results showed clearly that the cells of the spleen and the white blood cells of the blood from an allergic animal were killed by amounts of tuberculin in which normal cells grow freely and that the plasma of allergic animals had no effect in making normal cells susceptible to this effect of tuberculin.

Antibody Production in Tissue Culture.—The first more or less direct proof of the part played by the reticuloendothelial cells in antibody production has been given in a report by MEYER and LOEWENTHAL (*Ztschr. Immunitätsforsch. u. Exper. Therap.*, 1928, 54, 409). Agglutinins were regularly observed in tissue cultures of the spleen, lymph glands and the milk spots (milchflecken) of the omentum of rabbits after the antibody production was started by injections of killed cultures of B. typhosus or after the bacteria had been brought into intimate contact with the tissues by an intravenous injection directly before the animal was killed. The agglutinins were demonstrable in forty-eight hours, reached their maximum in three days, and then dropped off rapidly. Since some of these cultures contained, besides fibroblasts, only cells of the reticuloendothelial system, this was taken as evidence that these latter were responsible for the antibody production.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

The Public Health Organization of Denmark.—PARRAN (*Pub. Health Repts.*, 1927, 42, 1417) introduces the subject by noting the density of population, the high standards of living and the relative absence of poverty. The mortality rate is favorable—about 12 per 1000—and the average life expectancy is fifty-eight years. Major infectious diseases have very low rates. There are a few full-time medical health officers and many engaged on a part-time basis. There is approximately 1 physician to 1600 of the population. Quackery has been prohibited since 1672. Only 20 per cent of medical service is "private practice," the remainder is through sick benefit clubs and governmental agencies. The hospital service is well developed and the public health movement centers around this and the practising physician. Hospital beds number 4.5 per 1000 population. An average of 1.4 days is spent in hospitals each year by the whole population compared with 0.61 in the United States. There is 1 bed per 1000 population for contagious cases and hospitalization is nearly uniformly carried out. Smallpox is unknown, except for imported cases, as vaccination has been compulsory for over a century. The tuberculosis death rate is the lowest for any country and hospitalization of tuberculous cases is general. The Finsen light treatment for skin and surgical tuberculosis is very popular. Free treatment is provided for any venereal disease patient, and treatment is obligatory. There are in the country about 1000 hospital beds for venereal disease. Sick benefit insurance covers 60 per cent of the population between fifteen and sixty years, and children of beneficiaries are treated. Social and welfare activities are discussed. Milk control is vested in the various municipalities. There is less pasteurization and less attention to bovine tuberculosis than in the United States. The article concludes: "What, in brief, impresses the public health student in Denmark? The complete, elaborate and expensive provisions which are made for the care of the unfortunate members of society are constantly noticed. The splendidly organized system of curative medicine, under which medical, hospital, dental, nursing, sanatorium, asylum, in fact every type of care is furnished to all in need thereof free, or at a cost within the ability of all to pay, forms the backbone of the public health system. Much consideration is given to child welfare, to the crippled, the blind, the deaf, the scrofulous, the illegitimate, the orphan, to the aged, to the insane, and even to the criminal. The sickness, unemployment, accident, old age and burial

insurance systems are most complete. The high standards of education and the absence of illiteracy, the even distribution of wealth and the absence of extreme poverty and slums, are striking. There is a uniformly high standard of medical, dental, nursing, pharmaceutical and midwife education. The physicians are held in high public esteem; there is an absence of quackery and the economic and social position of the physicians is comparatively good. The physical vigor of the people is noticeable and undoubtedly is related to their passion for physical training as well as to the racial stock and their economic and social progress. A coöperative spirit everywhere is manifest; this is so basically a part of their nature that it is reflected not only in their whole social system, but even in the games which the children play. Along with this spirit of mutual self help, individual initiative and responsibility have been developed with the result that their highly developed and complicated social order seems to have been evolved by and for the people themselves, and not to have been imposed upon the country by some central authority or by some one class of the people."

The Diagnosis of Poliomyelitis.—LEAKE (*U. S. Pub. Health Repts.*, 1927, 42, 2431) states "Acute poliomyelitis is a name given to a specific infectious disease which sometimes, but not usually, results in paralysis." "Infantile paralysis" is incorrect as it is by no means rare in adults. The *systemic* symptoms may simulate any indefinable illness; the onset is often insidious, but may be abrupt. Vomiting, abdominal pain, or constipation may occur. Drowsiness is common, though the reverse may occur. Retention of urine and sweating are significant. Sorethroat may occur. *Meningeal* symptoms are chiefly pain on anterior flexion of the spine, hyperesthesia and increased reflexes. Lumbar puncture shows a clear fluid free of organisms, increased cells, albumin and globulin. The tenderness may be superficial or elicited by deep pressure. There may be joint pain developed on motion. Tremor is often noted. There is increase of patellar and other reflexes in this stage. *Paralytic* symptoms: General weakness out of proportion to the fever is often seen before any definite localization. The paralysis is typically flaccid. The legs are involved more often than any other region; the arms, particularly the deltoid muscle, next. The external rectus of the eye is the most commonly involved of the head muscles. Paralysis of throat muscles is of serious import. Death is usually due to respiratory paralysis.

The Unexplored Field of Preventive Medicine in Private Practice.—DRAPER (*U. S. Pub. Health Repts.*, 1927, 42, 2241) believes that public health functions have come into the hands of official agents (1) because the general practitioner is not trained in preventive medicine, and (2) concerted action by a central official agency is often necessary. It is pointed out that the development of public health activities has been due to the medical profession and that larger opportunities lie in the future.

Seasonal Incidence of Tularemia and Sources of Infection.—The PUBLIC HEALTH SERVICE (*U. S. Pub. Health Repts.*, 1927, 42, 2948) emphasizes the three sources of infection, the tick bite, the fly bite and the dressing of wild rabbits. Any wild rabbit seems to suffice as

a reservoir of infection. Dressing of wild rabbits seems to be the most common source of the infection, and cases traceable to these occur in the "open season." Tick-bite cases occur from March to August, the season of greatest activity of ticks. Cases of fly origin occur from June to September, the period of greatest activity of horse flies. Market men are often infected from dressing or handling the carcases of rabbits. The case fatality rate is 4 per cent. One attack confers immunity. There is no serum or vaccine of value, nor has any special drug been found effective. Rubber gloves should be worn by those dressing wild rabbits. Cooking rabbit meat makes it safe. The final paragraph concludes the paper as follows: "Finally, beware of the wild rabbit which the dog has caught, or which the boy has killed with a club—it is probably a sick rabbit. The hunter should not shoot the rabbits at the point of his gun; let him be a sportsman and shoot them on the run at 75 yards, say, and the chances will be lessened that the rabbits he bags will be sick with tularemia."

Endemic Goiter in Oregon.—OLESEN (*U. S. Pub. Health Repts.*, 1927, 42, 2831) reports that among boys the incidence of thyroid enlargement was 22.3 and 38.3 per cent among girls. Among these about 10 per cent of each sex among those afflicted showed adenomata. Even on the seacoast, where goiter usually is infrequent, it was found fairly common in Oregon. In boys the highest incidence occurs at thirteen years; in girls the highest was eighteen years. Nothing was found to support the view of McCarrison that polluted water was to be held responsible for goiter in the area studied.

An Analysis of Infant Mortality by Causes.—GREEN (*J. Prev. Med.*, 1927, 1, 391) declares that infant mortality has been greatly reduced during the past generation. The decrease in the number of deaths due to diarrhea and enteritis is largely responsible for this reduction. The death rate from premature birth has steadily increased during the past generation, until now it has replaced diarrhea and enteritis as the most important cause of infant mortality.

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All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be at the end of the article and should be complete, that is, author's name, title of article, journal, year, volume (in Arabic numbers) and page (beginning and ending).

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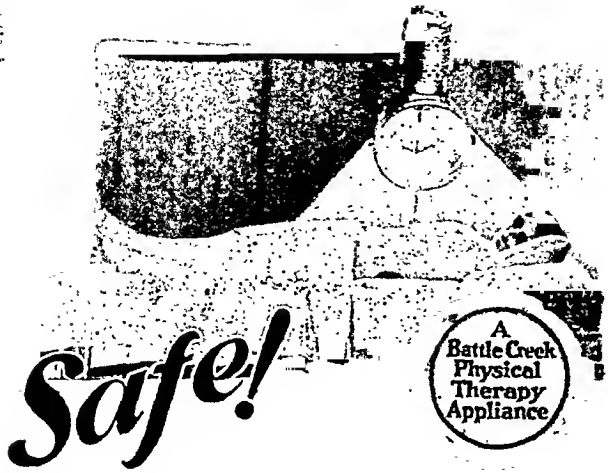

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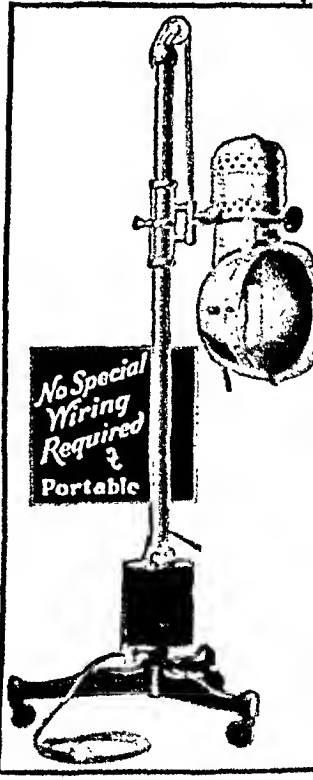

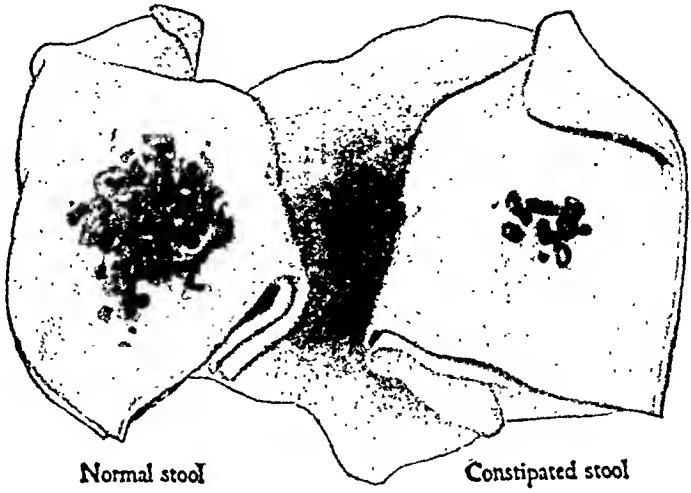

Normal stool Constipated stool

INFANCY AND CHILDHOOD

A *RECENT census* shows that 20% of all deaths were children under five years. Twenty-nine percent of the deaths of children under one year were of intestinal origin. At least 50% of the ills of infancy and childhood are due to intestinal affections, says a noted gastroenterologist.

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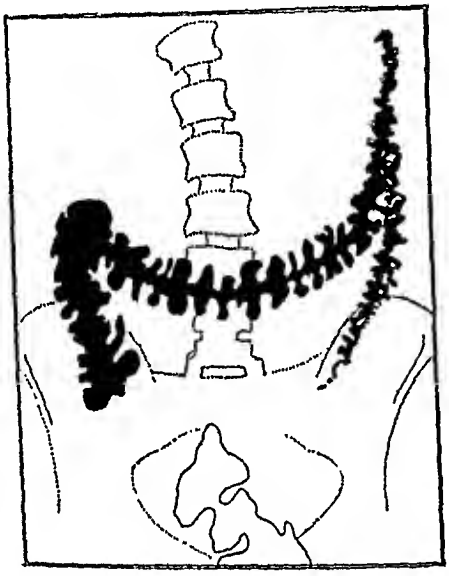
Occult Constipation



Occult constipation (from an X-ray) 24 hours after opaque barium meal. There has been one small stool as usual. Note the deep haustrations and partial dilatation of cecum

THE menace of occult constipation lies in the fact that the patient may have regular daily evacuations, and is therefore unaware of the constant retention of fecal matter, which may ultimately form a hard and deep coating on the intestinal wall, leaving but a small passage through which painful and partial evacuation takes place.

When headaches, lassitude, and the conditions usually associated with the development of intestinal toxemia lead to the suspicion of hidden constipation, the reliance of many physicians is on AGAROL, *the original mineral oil and agar-agar emulsion.*

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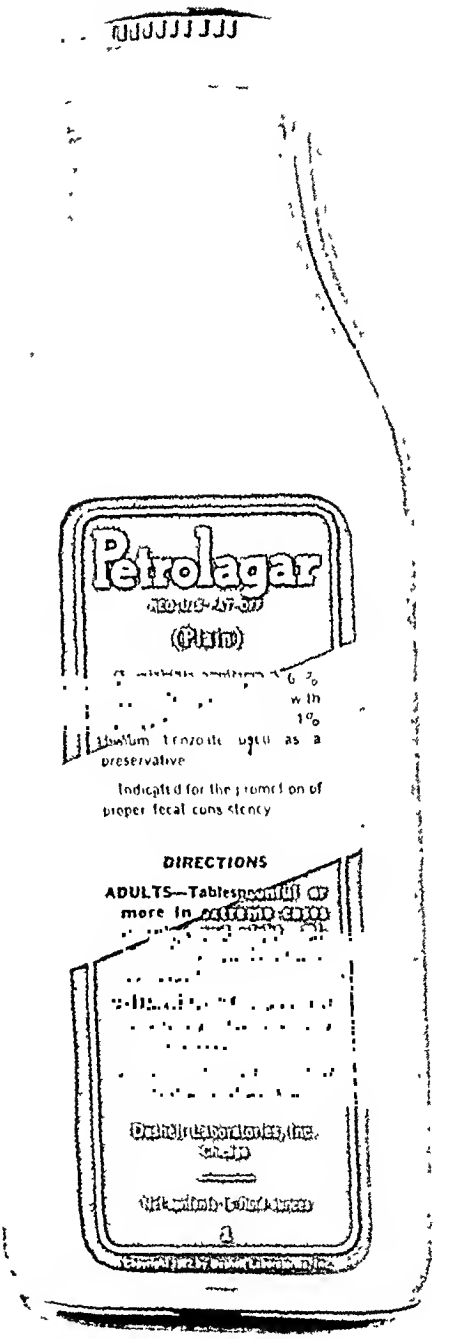
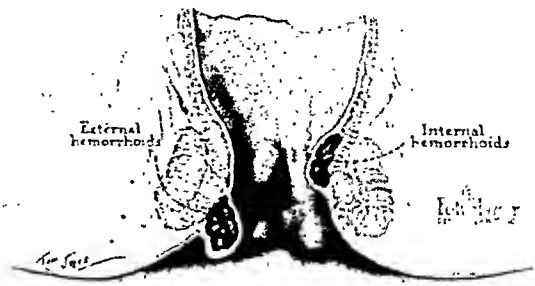


CANCER OF BOWEL



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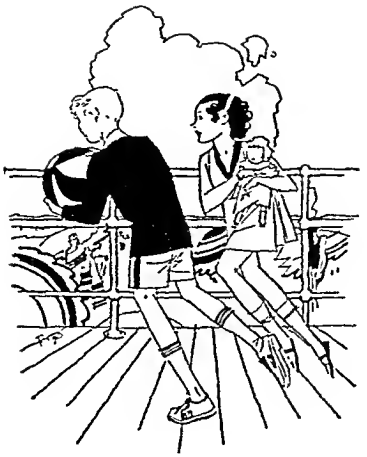

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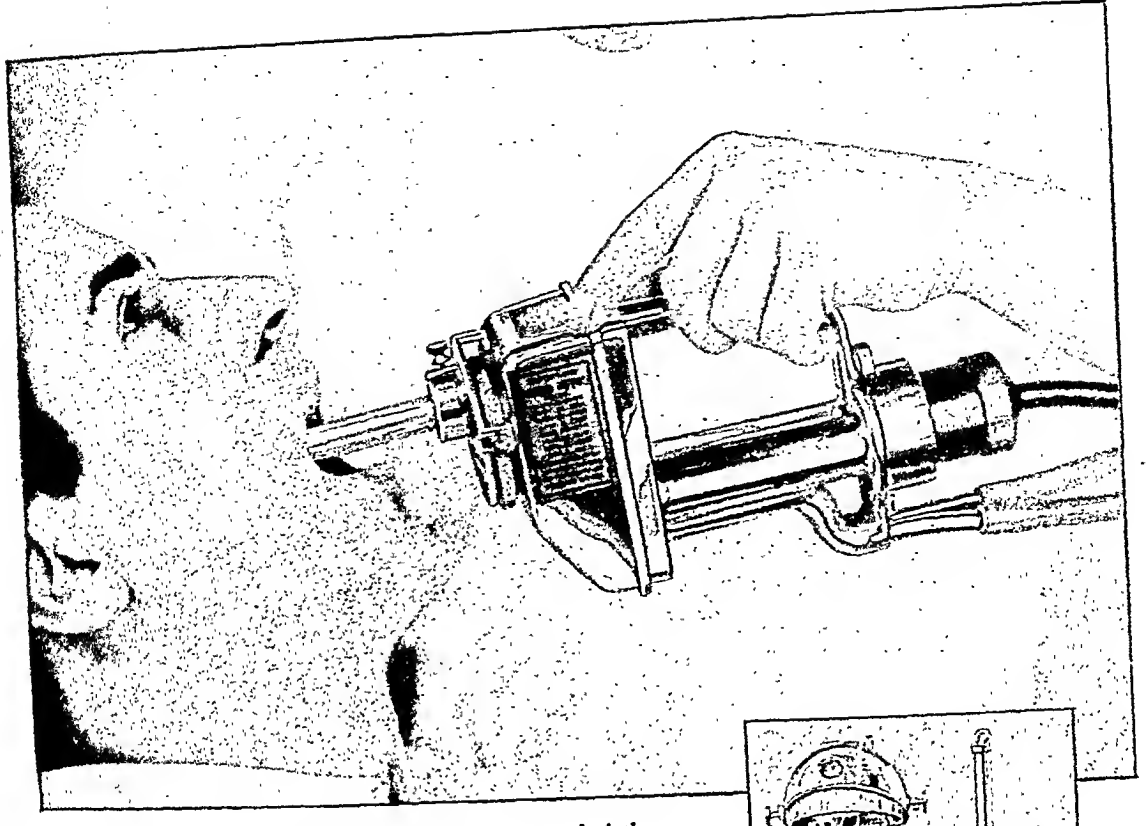

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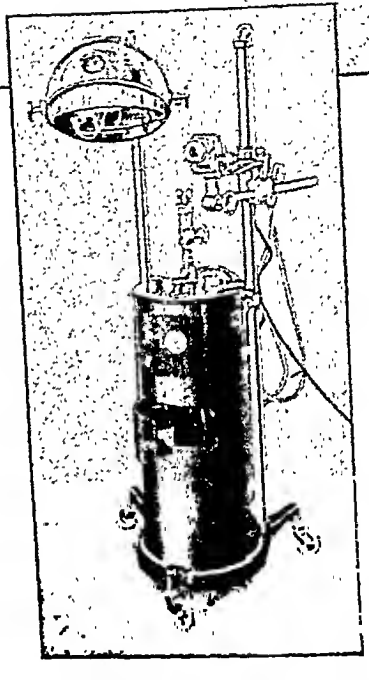

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